PANCREATITIS

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A CLINICAL PATHOLOGIC CORRELATION

By

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To

Mr Morton J May

Whose Continuing Interest Loyalty and Support

Have Sustained Our Research on Pancreatitis for

Over a Quarter of a Century

FOREWORD

Interest in pancreatitis from both the clinical and research point of view is greater today than any time since the classic description of the pathology of this disease by Reginald Fitz of Boston in 1889 The frequency of pancreatitis was suspicioned by Fitz but it lacked documentation until Somogyi developed a practical diagnostic method of determining blood diastase activity

Slowly but surely the more widespread and routine use of this test day or night in all cases of abdominal pain has shown pancreatitis to be a major consideration in the differential diagnosis of the acute abdomen Since 1903 most studies have been directed toward challenging or championing the idea of the common channel of Opie as the etiological factor responsible for the production of this serious disorder Despite these and other monumental contributions the fact remains that the morbidity and mortality associated with either acute or chronic pancreatitis remains higher than other common diseases involving the gastrointestinal tract This unsatisfactory state of affairs has stimulated the clinician investigator and pathologist along with others to intensify their efforts to learn more about pancreatitis

The treatment of a disease becomes more effective when the cause is known so an increasing effort is being directed toward producing pancreatitis experimentally in animals and attempting to coordinate these observations with the studies of the pathology found in patients Biliary tract disease alcoholism and over indulgence in caffeine containing drinks have long been suspicioned as leading etiologic factors but they certainly do not explain the cause in all cases Not clearly understood is the effect of liberation of the various powerful digestive enzymes of the pancreas following blockage of the major duct or interference with its blood supply How important is the role played by these activated enzymes? Certain distinctive features in the pathology of this disease are directly due to them yet individually they

are not especially toxic in the amounts normally present in the pancreas Future studies may not only identify the type and extent of the enzyme activity but also may develop methods of neutralizing their destructive effect Measurement of intracellular enzymes liberated in the course of pancreatic destruction may become more helpful and specific diagnostically than amylase

While there is general agreement that the treatment should be directed toward placing the pancreas at rest by constant gastric suction and intravenous feeding the need for colloid replacement is not sufficiently appreciated Fluid not only weeps from the pancreas into the surrounding retroperitoneal tissues but also into the peritoneal cavity When paralytic ileus is present further losses occur into the distended intestine There also is evidence that an increased hemolysis of the red cells takes place making whole blood replacement essential as the hemoglobin falls

Less is known about etiology and treatment of the chronic forms of pancreatitis Fertile fields for study include the influence of other glands of internal secretion especially the parathyroids in the etiology of pancreatitis in the formation of pancreatic calculi and the tendency to a lowered blood calcium level The future may hold a method for visualizing the pancreas by x ray after the administration of a suitable dye More coordinated studies of the pancreas of the type presented in this book are needed to insure continued progress

Familiarity with the contents of this brief encyclopedia on pancreatitis will prove invaluable to the clinician as well as those interested in further research on diseases of the pancreas The significant landmarks in this disease have been digested and a tremendous bibliography on the etiology pathology and treatment have been indexed in the appropriate categories The normal as well as the pathologic physiology of the pancreas is presented in an interesting and authoritative manner This book represents in almost capsule form the sum knowledge as it now exists in medical science on the subject Investigators of diseases of the pancreas in the future will be ever grateful to the authors for this authoritative and thought provoking reference

Robert M Zollinger M D

PREFACE

Just over a quarter of a century ago Dr Michael Somogyi of our hospital was successful in developing a practical method for determining blood diastase activity suitable as a routine procedure in hospital laboratories This discovery made possible the accurate diagnosis of acute pancreatitis and the study of this disease in hospital patients With this as a stimulus there developed over the ensuing years a program of research in pancreatitis at the Jewish Hospital of St Louis

During the first part of this period studies dealt with a clinical evaluation of the significance of blood and urinary diastase levels and were carried out under the direction of the late Dr S H Gray with Drs J G Probstein C J Heifetz and L A Sachar as collaborators Later attention was directed to certain of the clinical characteristics of acute pancreatitis to considerations of differential diagnosis and therapy and to diseases which might bear a causal relation to acute pancreatitis Experimental as well as clinical studies were carried out and in these the late Dr P A Wheeler and Drs S Russi and W Rindskopf also participated

In more recent years attention has turned to the sequelae of acute pancreatitis and to certain etiologic considerations particularly as regards the role of vascular alterations in the pancreas Drs R A Joshi J G Probstein and H T Blumenthal have collaborated in these studies Supplementary material for certain of the studies dealing with the sequelae of acute pancreatitis were obtained from Washington University and the Homer G Phillips Hospital and for these cases we are indebted to the late Dr Robert Elman

This monograph is an outgrowth of the foregoing program It is intended primarily as a clinical pathological correlation based solely on autopsy material Experimental studies are considered only insofar as they relate to clinical problems While the volu

minous literature on pancreatitis has been carefully studied di rect reference has been made only to certain particularly perti nent articles and to reviews which have coverage of the extensive bibliography existing in this field

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PANCREATITIS

INTRODUCTION

Medical thinking appears to have frequently been handicapped by the unitarian philosophy whereby a single etiology has been sought to explain a particular disease In large part this is a hangover from the era of bacteriology when specific infectious diseases could be attributed to particular infectious agents In non infectious diseases such thinking usually derives from a consideration of end stage pathologic changes as represented by a single disease entity and therefore due to a single cause or group of closely related causes The fallacy in such an approach lies in the failure to recognize that tissues and organs have the potential to react to a diversity of injurious agents in only a limited number of ways Thus a wide variety of inflammatory agents infectious and non infectious may evoke an identical early response in a particular organ abnormal physiological processes a different one and degenerative vascular diseases still another type of reaction In the end stage however it may be impossible to distinguish between these three groups of etiologic factors on the basis of gross or microscopic anatomical changes

Such considerations are particularly pertinent as regards acute inflammation of the pancreas for not only are the foregoing considerations as regards the end stage lesion applicable but the nature of this particular organ is such that even intermediate alterations may be identical in instances in which diverse etiologic factors may obtain This is so because the pancreas contains proteolytic amylolytic and lipolytic enzymes which may be released into the interstitial tissues as a result of the action of a variety of unrelated injurious agents and proceed to produce an inflammatory reaction and to destroy not only parenchymatous elements but also supporting structures and vasculature The result is necrosis of parenchyma fat necrosis inflammatory cell infiltration and hemorrhage in varying proportions To a considerable degree early reports of pancreatitis show an appreciation of such considerations

According to Opie the monograph by Friedreich containing the meager clinical information published before 1875 appears to have been the first attempt at a systematic description of pancreatic disease Friedreich apparently utilized monographs by Classen (1842) and Ancelet (1866) as well as the carefully described cases and pathologic records collected by Cruveilhier Rokitansky Virchow Klebs and others He also had available at that time a dissertation by Claude Bernard on the role of the pancreatic secretions in the digestion of proteins fats and carbohydrates

Friedreich and later workers apparently believed that the symptoms produced by lesions of the pancreas were so ill defined that the diagnosis of pancreatic disease was impossible Nevertheless he described acute primary pancreatitis acute secondary pancreatitis (parenchymatous degeneration) and chronic pancreatitis and he further recognized the frequently hemorrhagic character of the acute inflammatory reaction In 1899 Fitz proposed a classification of acute pancreatic disease in which he distinguished three types of inflammation — hemorrhagic gangrenous and suppurative pancreatitis and described the symptomatology accompanying each Interestingly he recognized that these lesions had features peculiar to the pancreas and not produced by disease of similar character in other organs It is now recognized that these differences which were then obscure are dependent upon those physiologic peculiarities of the pancreas noted above and which make necrosis and hemorrhage such important components of acute pancreatitis

The initial recognition of fat necrosis is usually attributed to Balser (1882) Subsequent studies by Fitz Chiari R Langerhans Hildebrand and Dettmer and others showed that this was not a single disease condition but a consequence of a variety of pancreatic lesions

One further noteworthy contribution to the classification of inflammatory disease of the pancreas was introduced While the prominence of the hemorrhagic component of certain cases of acute pancreatitis had already been described by Rokitansky and by Klebs certain distinctions regarding this hemorrhage remained

to be clarified Spiers (1866) first described a specific hemorrhagic condition of the pancreas in individuals previously supposed to be in good health in which the illness lasted only a few hours and invariably terminated fatally The quantity of blood escaping from the vessels did not bear a direct relation to the severity of the lesion Zenker Prince Draper and Seitz subsequently reported additional instances of this condition which came to be known as pancreatic apoplexy and likened to cerebral apoplexy Most workers of that period believed that hemorrhage into the substance of the gland might be caused by a variety of factors which were not peculiar to the pancreas and could be found in other tissues of the body They based this conclusion on the fact that trauma and tumors of any organ might cause vascular rupture or erosion and that the content of pancreatic cysts were not infrequently bloody They were also aware of the occurrence of minute hemorrhages in association with purpura eclampsia and certain infectious diseases which are dependent upon factors that determine their occurrence in other organs as well as the pancreas and have little in common with the peculiar hemorrhagic lesion to which the pancreas is subject But Seitz pointed out that in some reports of death associated with poisoning or trauma in which a diagnosis of pancreatic apoplexy had been made the extravasation of blood may have been the result of postmortem autodigestion It is also pertinent that Fitz cited the observation that fluids injected into the arteries of a dead body are prone to escape into the region of the pancreas and Klebs recognized the possibility that hemorrhage occurring in the absence of inflammatory changes might be due to the corrosive action of the pancreatic juice upon blood vessels during life a view which was later expressed by Rich and Duff Seitz maintained that in a limited number of cases arteriosclerosis explained the occurrence of hemorrhage but Opie felt that the only evidence to support this was the occasional association of the two conditions

A less severe form of acute pancreatitis was first described by Halsted (1890) and later by Billard and Branca (1909) and by Mercade (1919) This condition was later referred to as acute pancreatic edema by Zoeppfel as "subacute pancreatitis by

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of Doublet and Mulholland have influenced studies in the direc tion of determining the effects of such causes on the impedance to the outflow from the biliary and pancreatic ductal systems and the interplay of bile and pancreatic secretions in the patho genesis of acute pancreatitis While there is no intent to minimize the importance of these studies it should be pointed out that they have had the effect of encouraging the use of surgical procedures directed at correcting a presumed obstruction in the biliary pancreatic ductal system even in cases in which direct proof of such impedance is lacking

Dragstedt has recently pointed up the importance of a bal anced perspective in this regard in the statement that it seems likely that most of the fatal cases of acute pancreatitis are due to a sudden extensive necrosis of the pancreas resulting from the passage of bile into the pancreatic ducts trauma to the pancreas interference with the blood supply or a combination of these factors occurring when the pancreas is actively secreting" He goes on to state that "it ought not to be concluded that when one method for producing pancreatic necrosis is demonstrated to be operative in one patient or even a group of patients that this method is necessarily operative in all"

For this study we have adopted a classification of precipitat ing causes which take into account known and hypothetical factors and which in our opinion maintains a balanced perspec tive In utilizing this outline we have attempted to show wherein these factors may affect the biliary pancreatic ductal systems as well as situations in which they may act independently of the latter This classification appears under etiology in Part I

The usual order for presenting a Clinical Pathological Correla tion i e a presentation first of the clinical features followed by a correlation with the pathologic findings has been reversed After dealing with certain statistical considerations and their relation to clinical and experimental work as regards etiology in Part I we have presented the pathologic physiology of acute pancreatitis in Part II Part III consists of a presentation of the pathology of this disease and Part IV deals with a reconstruction of the clinical manifestations as they relate to the evidence presented in

Stetten and as acute interstitial pancreatitis or acute transient disease of the pancreas by Elman The recognition of this milder form was at first based on observations at surgery or at autopsy and described as being characterized by a complete lack of necrosis However this apparently benign form of acute pancreatitis lacked real clinical definition until the serum amylase relationships had been worked out and reported by Elman Bachy Dragsted Haymond and Ellis Penin Vianna Moirud and Dor May and Mahner and by Gray Probstein and Heifetz

Apparently taking his cue from Opie whose work had firmly established the Common Channel Theory Archibald suggested that this lesion was initiated by a reflux of bile into the pancreatic ducts while Elman attributed it to transient obstruction of the main pancreatic duct Zoeppfel Stetten Bachy Penin and Nordmann all believed it to be an early *stage of acute necrosis* While agreeing with this Schmieden and Sebening Archibald Leveuf and May felt that this lesion did not invariably progress to necrosis but frequently subsided without the development of this complication On the other hand Walzel and also Polya believed this condition to be a benign lesion unrelated to acute pancreatic necrosis which subsided spontaneously

There has been reported in addition an apparently asymptomatic type of acute pancreatitis which is encountered at autopsy as an incidental finding Balser Langerhans Chiari Williams and later Opie all described foci of fat necrosis in the pancreas at autopsy in patients without clinical evidence of pancreatic disease More recently Burn and also Sachar and Probstein have again directed attention to this incidental finding and have emphasized the importance of circulatory factors

As a recognition of these characteristics which are peculiar to acute inflammation of the pancreas have evolved investigations have also been conducted on precipitating causes Dragstedt Hayward and Ellis in an extensive review have covered the earlier work in this area and such causes will be discussed in appropriate sections While a multiplicity of precipitating causes have been recognized the stimulus of Opie s important work on the Common Channel Theory and the impact of the observations

PART I

BASIC STATISTICAL CONSIDERATIONS AND THEIR SIGNIFICANCE

Parts II and III Finally Part V deals with the therapy of acute pancreatitis Appropriate considerations as regards sequelae are dealt with in each part

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Chapter 1

INCIDENCE, AGE AND SEX DISTRIBUTION, AND ETIOLOGIC CLASSIFICATION

1) *Incidence* As Ivy and Gibbs have pointed out meaningful reports on the incidence of pancreatitis are quite meager, but it does appear likely that the frequency is greater than one would judge from routine clinical experience In 1939 at a hospital in Detroit the incidence was reported as one in 10 000 admissions while at the Jewish Hospital of St Louis in 1949 following a period during which a serum amylase determination was carried out routinely as part of each admission work up the incidence was found to be about one in 600

The incidence of acute necrotizing pancreatitis in an autopsy series of 41 333 cases reported by McWhorter in 1952 was 0 387 per cent or approximately four per thousand The incidence in the present study based on a series of 3665 autopsies was 4 4 per cent or approximately 44 per thousand over ten times the incidence found by McWhorter However this includes many mild cases which were evidently subclinical and in which acute pancreatitis constituted an incidental autopsy finding Of the 163 cases of acute pancreatitis in the present study only 17 were of such severity as to be considered the primary cause of death or an incidence of 0 46 per cent a figure which is comparable to that found by McWhorter This is the equivalent of 2 8 per 600 or over 2 5 times that reported previously from this hospital based on clinical and laboratory findings

A determination of the frequency of chronic pancreatitis appears to be extremely uncertain if not impossible even in an autopsy series and it has not been attempted here As pointed out in Part III it is extremely difficult even to establish histologic criteria for diagnosing such a condition and the suspicion of such a lesion based on microscopic findings would have to be closely correlated with a clinical history covering a long period of time Such long term patient histories are notoriously unreliable unless

b) *Age and Sex Distribution* Information in this regard is also quite meager Recently Bell found an incidence of fatal pancreatitis in an autopsy population of 0.25 per cent in men over age 20 and 0.36 in women in the same age range Based on the percentage of deaths the maximum incidence was found to occur in the third and fourth decades in men and in women in the fifth and sixth decades Bell found a sex ratio corrected for the preponderance of men as roughly three women to two men

The age distribution of pancreatitis and the other common degenerative diseases has been analyzed here in two ways (1) on the basis of peak age incidence of all cases of a particular disease and (2) on the basis of the percentage of such cases in the total autopsy population in the same decade In the first type of analysis all the diseases listed in Table 1 showed a peak incidence between 51 and 70 years followed by some diminution in frequency in succeeding years There were differences however when the second method was applied Myocardial infarction and cerebral infarction or hemorrhage showed a progressive rise in incidence with each succeeding decade after age 50 while all of the others showed an almost constant frequency in each decade after age 50 The latter data therefore show that except for the complications of cardio and cerebrovascular disease the frequency distribution curve only parallels the age distribution curve for the total autopsy population

TABLE II

Age and Sex Distribution in Acute Pancreatitis

Age Group	*Without Pancreatitis* Male	Per Cent	Female	Per Cent	*With Pancreatitis* Male	Per Cent		Female	Per Cent	
0-10 yrs	312	15.7	183	12.1	5	5.3	(1.6)	1	1.4	(9.5)
11-20 yrs	23	1.2	25	1.7						
21-30 yrs	42	2.1	59	3.9	1	1.1	(2.3)	3	4.3	(4.8)
31-40 yrs	96	4.8	117	7.7	7	7.4	(6.8)	2	2.9	(1.7)
41-50 yrs	210	10.5	175	11.6	15	16.0	(6.7)	12	17.4	(6.8)
51-60 yrs	436	21.9	336	22.2	16	17.0	(3.7)	8	11.6	(2.3)
61-70 yrs	496	24.9	347	23.0	28	29.8	(5.4)	20	29.0	(5.4)
71-80 yrs	302	15.2	196	13.0	20	21.3	(6.2)	17	24.6	(8.0)
81 +	75	3.8	72	4.8	2	2.1	(2.6)	6	8.7	(7.7)
Total	1992		1510		94		(4.5)	69		(4.4)

Figures in parenthesis represent per cent of autopsy population in corresponding decade and sex and in bottom horizontal column per cent of total autopsy population of corresponding sex

the patient has been under close scrutiny of a physician for many years

In Table I we have compared the frequency of acute pancreatitis with other common degenerative diseases Acute pancreatitis was found to be about one fifth as common as myocardial infarction and about one third as frequent as non traumatic cerebrovascular hemorrhage or infarction It was about one sixth as common as cancer and about one half as frequent as diabetes The frequency of acute pancreatitis was equal to about that of renal uremia and about four times more common than gangrene of the intestines or of the lower extremity

TABLE I

COMPARATIVE FREQUENCIES OF COMMON DEGENERATIVE DISEASES

Age Group	*Myocardial Infarction*		*Cerebral Infarction and Hemorrhage*		*Intestinal Gangrene*		*Extremity Gangrene*	
	No	*Per Cent*	*No*	*Per Cent*	*No*	*Per Cent*	*No*	*Per Cent*
0 10 yrs		( )		( )	4	*7 0 (0 8)*		( )
11 20 yrs		( )	1	0 3 (2 1)		( )		( )
21 30 yrs	2	0 2 (2 0)	4	1 2 (3 9)	1	1 8 (1 0)		( )
31 40 yrs	15	1 8 (7 0)	12	3 5 (5 6)	3	5 3 (1 4)		( )
41 50 yrs	63	7 7 (16 4)	32	9 3 (8 3)	5	8 8 (1 3)	2	3 8 (0 5)
51 60 yrs	210	25 6 (27 2)	79	23 0 (10 2)	15	26 3 (2 0)	15	28 8 (1 9)
61 70 yrs	283	34 6 (33 6)	113	32 8 (13 4)	13	22 8 (1 5)	18	34 6 (2 1)
71 80 yrs	182	22 2 (36 5)	78	22 7 (17 4)	13	22 8 (2 6)	13	25 0 (2 6)
81 +	64	7 8 (43 5)	25	7 3 (17 0)	3	5 3 (1 4)	4	7 7 (2 7)
Total	819	(22 4)	344	(9 4)	57	(1 6)	52	(1 4)

Age Group	*Renal Uremia*		*Diabetes*		*Malignant Disease*		*Acute Pancreatitis*	
	No	*Per Cent*	*No*	*Per Cent*	*No*	*Per Cent*	*No*	*Per Cent*
0-10 yrs	3	2 0 (0 6)	1	0 3 (0 2)	13	1 3 (2 6)	6	3 7 (1 2)
11 20 yrs	2	1 4 (4 2)	3	1 0 (6 2)	11	1 1 (23 0)		( )
21-30 yrs	9	6 1 (8 9)	4	1 4 (4 0)	18	1 8 (17 8)	4	2 5 (4 0)
31-40 yrs	16	10 9 (7 5)	17	5 9 (8 0)	76	7 6 (35 7)	9	5 5 (4 2)
41 50 yrs	21	14 3 (5 5)	23	8 0 (6 0)	138	13 9 (35 8)	27	16 6 (7 0)
51 60 yrs	37	25 2 (4 8)	69	24 1 (8 9)	285	28 6 (36 9)	24	14 7 (3 1)
61 70 yrs	39	26 5 (4 6)	106	37 1 (12 6)	268	26 9 (31 8)	48	29 4 (5 7)
71 80 yrs	*13*	*8 8 (2 6)*	52	18 2 (10 5)	143	14 4 (28 7)	37	22 7 (7 4)
81 +	7	4 8 (4 8)	11	3 8 (7 5)	44	4 4 (30 0)	8	4 9 (5 4)
Total	147	(4 0)	286	(7 8)	996	(27 2)	163	(4 4)

All traumatic cases eliminated

Cranial examination permitted in only about 65 per cent of necropsies Correction would increase number in this group to about 521 or a frequency of about 14 5 per cent in the total autopsy population

Figures in parenthesis represent per cent per decade and in bottom horizontal column per cent of total autopsy population

Chronic relapsing or acute recurrent pancreatitis is even more uncommon in infancy and childhood Comfort Gambill and Baggenstoss found only two of their 29 cases reported in 1946 in children and Collett and Kennedy have since added a third the latter associated with hyperlipemia

Thus the six cases included in the present series represent a significant contribution to the literature numerically There were 5 males ranging in age from two days to two weeks and one female child three years of age Etiologically these cases fall into three groups metabolic infectious and idiopathic and they will be considered in appropriate sections We have not included fibrocystic disease of the pancreas since if this is to be considered a form of pancreatitis it is a special type

c) *Etiologic Classification* After careful consideration of the literature relative to etiology we have devised the following classification which includes proved as well as hypothetical factors

Classification of Acute Pancreatitis Based on Etiology

1 *Infectious Agents*
   a) Invasion from blood stream and septic emboliza tion
   b) Lymphatic spread from the gallbladder common duct or ampulla of Vater
   c) Tissue spread from duodenal ulcer duodenitis peritonitis of infection of common bile duct or ampulla of Vater
   d) Activation of bacteria normally present in the gland

2 *Obstructive Disease of the Biliary and/or Pancreatic Duc tal Systems*
   a) Stone low in the ampulla of Vater (Common Channel)
   b) Spasm or edema of the sphincter of Oddi or of the papilla of Vater (Common Channel)
   c) Duodenal diverticula and other anomalies

The data in Table II show that there is an essentially equal overall incidence of acute pancreatitis in the two sexes and in fact this equality has carried through in large part when the figures are analyzed by decade With regard to the latter the incidence in each sex in the decades after 50 years varies between 2 6 and 8 8 per cent It is doubtful if this variation is of any significance with the possible exception of the decade 51 60 where a low figure was obtained in both sexes The low figure in the last age group may not be significant because of the small number of cases At any rate in the age group 61 80 the incidence by decade varies only between 5 4 and 8 0 per cent The approximate equality of sexes as regards incidence is in agreement with most reports

These data further show that acute pancreatitis may be found in all age groups including newborn infants with the greatest number of cases in the decade 61 70 and this again follows the age distribution curve for the total autopsy population The occurrence of acute pancreatitis in infancy and childhood deserves some emphasis because it is believed to be extremely rare in this age group Opie casually mentioned a fetal form due to congenital syphilis but as late as 1956 Gibson and Gibson were able to collect only 27 published cases and added one of their own Pancreatitis associated with mumps has been recognized for many years but some childhood cases have also been associated with scarlet fever diphtheria typhoid fever influenza otitis media or trauma In this group of 28 cases there were also included two cases which had been reported by Dobbs in which obstructive disease of the biliary pancreatic ductal system was found one of these was associated with gallstones and the second with round worms obstructing the pancreatic ducts Four additional cases were reported during 1957 two by Baar and Wolff and one each by Marczynska Robowska and by Pender in all but one of which cortisone therapy appeared to be the causal agent In addition to these 32 cases Steiner and Tracy have reported an association between pancreatitis and diabetic coma in 10 children examined postmortem and have cited four other cases of pancreatitis among 20 children who had also died in diabetic coma

After careful study of the autopsy material and clinical histories of the 163 cases of acute pancreatitis we have divided those in which a definitive etiology could be determined with reasonable certainty from the remaining cases in which no evidence for a distinctive etiology could be found These have been tabulated in Table III in order of frequency It is evident that over one third of the cases belong in the last category and these we have classified as "idiopathic" They have been separately analyzed for indirect evidence as to etiology and have been presented at the end of this section

- d) Spasm or edema of the sphincter or papilla of the pancreatic duct
- e) Ascarides
- f) Tumor or calculi obstructing the pancreatic ducts
- g) Epithelial metaplasia of pancreatic ducts
- h) Surgical ligature

3 *Metabolic Toxic and Chemical Factors*

- a) Liver disease
- b) Nutritional factors
- c) Toxic and chemical irritants
- d) Alcoholism
- e) Diabetes
- f) Hyperlipemia
- g) Hormonal factors
- h) Pregnancy
- i) Uremia

4 *Traumatic Factors*

- a) Accidental
- b) Surgical
- c) Electric shock

5 *Vascular Factors*

- a) Venous stasis and thrombosis
- b) Arterial occlusion
- c) Rupture of an arteriosclerotic vessel (Pancreatic Apoplexy)
- d) Arterial spasm

6 *Allergic*

7 *Idiopathic*

TABLE III

THE FREQUENCY OF VARIOUS ETIOLOGIC TYPES OF ACUTE PANCREATITIS

Etiologic Type	*Total*	*Male*	*Female*	*Per Cent*	*Age Range*
Idiopathic	57	29	28	35 0	22 90 Years
Infectious	32	20	12	19 6	Newborn 95 years
Vascular	22	16	6	13 5	30 82 years
Biliary Obstructive	17	10	7	10 4	45 93 Years
Metabolic Toxic and Chemical	18	13	5	11 0	3 days 70 Years
Traumatic	9	3	6	5 5	58 74 Years
Pancreatic Obstructive	7	3	4	4 3	30 65 Years
Allergic	1		1	0 6	28 Years
Total	163	94	69		

Nine of the 32 cases presumed to be on an infectious basis were in association with a bacteremia In this group there were 7 males ranging in age from two days to 79 years and two females 3 and 95 years of age Gallbladder disease was encountered in only the older female and there was no evidence of an inflammatory process of the major biliary or pancreatic ducts Diabetes was present in only one male and is mentioned only because of the recognized susceptibility to infection in this disease this case developed a bacteremia from a necrotizing papillitis of the kidneys Three of these cases were in elderly males who succumbed with a bacteremia shortly following a prostatectomy Three other cases developed blood stream invasion of bacteria complicating a lobar pneumonia two of these were in males ages 35 and 69 years and the third in the 95 year old female noted above In a two day old male infant septicemia was found in association with a meningococcic meningitis and in the three year old female child bacteremia and pancreatitis were terminal events in an acute lymphatic leukemia Almost all of these are old cases predating the modern use of antibiotics

b) ***Lymphatic Spread from the Gallbladder, Common Duct and Ampulla of Vater*** This mode of spread is based primarily on the frequent association of acute pancreatitis with gallbladder disease Deaver was one of the early workers to suggest that infection of the gallbladder or ducts might travel by way of the lymphatics to the pancreas producing acute pancreatitis Statistics available in the literature have been summarized by Ivy and Gibbs and show that chronic cholecystitis with cholelithiasis is more often associated with acute pancreatitis than is acute cholecystitis Thus only about 18 per cent of cases of acute cholecystitis are associated with acute pancreatitis while cholelithiasis has been found in from 40 to 80 per cent of cases of acute pancreatitis The figures in the present study are somewhat lower than these but the associations are similar There were 29 cases of acute cholecystitis in the total autopsy population 4 of which (13 8 per cent) were in association with acute pancreatitis the general autopsy incidence of acute cholecystitis was only 0 8 per cent All of the cases associated with acute pancreatitis were in males ranging in age from 56 to 85 Ivy and

Chapter 2

INFECTIOUS AGENTS

a) *Invasion from the Blood Stream and Septic Embolization*

The best evidence for this appears to exist in the rare cases of pancreatitis seen in children where it has been observed in association with mumps scarlet fever smallpox diphtheria malaria typhoid fever syphilis influenza pulmonary tuberculosis and otitis media (Brahdy and Scheffer Egdahl) The literature supporting this evidence has been cited in part in the preceding discussion of pancreatitis in infancy and childhood On an experimental level infectious pancreatic necrosis has been found in brook trout and in mice where it appears to be caused by the Coxsackie group of viruses (Wood Snieszko and Yasutake)

*In reporting 16 cases of acute pancreatitis in 54 patients re*ceiving ACTH and cortisone therapy Carone and Liebow found severe acute infections predominantly necrotizing pneumonitis and pyelonephritis in 15 In 4 of them a bacteremia was demonstrated but blood cultures were not obtained in the other 11 In two with staphylococcal septicemia clusters of gram positive cocci were demonstrated in the regions of exudation and fat necrosis

Of the 32 cases exhibiting evidence of an infectious agent 12 fall into this category Three of the latter group appear to be on a viral basis since they were associated with acute or subacute infectious hepatitis There were 26 cases of this type of hepatic disease in the total autopsy series so that the incidence of acute pancreatitis associated with it was 11 5 per cent All three cases *were in females ranging in age between 54 and 64 years and in* none of these was evidence of gallstones or inflammatory disease of the major hepatic or biliary ducts encountered Elman and Keating have also recorded this association If the virus of infectious hepatitis is a valid etiologic agent two routes of infection of the pancreas appear most likely (1) reflux of infected bile into the pancreatic ducts or (2) a viremia However a metabolic effect secondary to impaired liver function cannot be excluded as a possibility and such an effect will be discussed subsequently

more often than 13.8 18 per cent Nor does an analysis of the association of acute and chronic inflammatory disease of the liver with acute pancreatitis serve to clarify these problems Such an analysis is shown in Table V and the relationships are similar to those already commented upon with regard to the data in Table IV

TABLE V

INFLAMMATORY DISEASE OF THE LIVER AND ACUTE PANCREATITIS

	Without Pancreatitis				With Pancreatitis					
Age Group	*Male*	*Per Cent*	*Female*	*Per Cent*	*Male*	*Per Cent*		*Female*	*Per Cent*	
0 10 yrs	6	5.5	8	8.5	1	5.6	(14.3)	1	4.5	(11.1)
11 20 yrs			3	3.2						
21-30 yrs	3	2.7	5	5.3	1	5.6	(25.0)	1	4.5	(16.7)
31-40 yrs	10	9.1	11	11.8	2	11.1	(16.7)	1	4.5	(8.3)
41 50 yrs	12	10.9	6	6.4	3	16.7	(20.0)	4	18.2	(40.0)
51-60 yrs	27	24.5	21	22.3	4	22.2	(12.9)	3	13.6	(12.5)
61 70 yrs	37	33.6	17	18.1	3	16.7	(7.5)	4	18.2	(19.0)
71 80 yrs	12	10.9	17	18.1	2	11.1	(16.7)	5	22.7	(22.7)
81 +	3	2.7	6	6.4	2	11.1	(40.0)	3	13.6	(33.3)
Total	110	5.5	94	6.2	18	19.1	(14.1)	2[illegible]	31.9	(19.0)

Per cent of autopsy population without pancreatitis in corresponding sex group
Per cent of autopsy population with pancreatitis in corresponding sex group
Figures in parenthesis represent per cent of all cases of inflammatory disease of the liver in corresponding decade and sex and in bottom horizontal column per cent of total cases of corresponding sex with inflammatory liver disease

Nor is the relation of gallbladder infection to pancreatitis clarified by existing reports Maugeret Arnsperger Deaver and Sweet and Judd have all stated that bacterial infection may spread from the wall of a diseased gallbladder to the pancreas by ramification through the anastomosing network of lymphatics in the retroperitoneal tissue between the gallbladder and the pancreas However Kaufmann was unable to produce pancreatic *necrosis in experimentally induced acute bacterial cholecystitis* in animals and Wangensteen *et al* Grant and Sanchez Ubeda *et al* have pointed out the relative safety of either the non surgical or surgical treatment of acute cholecystitis because of the low frequency of associated pancreatitis Furthermore Kodama was unable to demonstrate lymphatic connection between the gallbladder and pancreas although there are such connections between the common duct and pancreas this observation certainly bears further scrutiny and study It may be that such

Gibbs have also stated that 18 per cent of cases of acute pancreatitis show acute cholecystitis in the present series the per cent showing this relationship was only 2 5 The data on chronic cholecystitis with cholelithiasis are shown in Table IV the frequency of chronic cholecystitis in cases with acute pancreatitis is twice as great as in the general autopsy population in males and is 2 5 times as common in females The frequency of chronic gallbladder disease in females with acute pancreatitis (45 6 per cent) corresponds to the low end of the range compiled by Ivy and Gibbs but it is considerably lower in males

TABLE IV

INFLAMMATORY DISEASE OF THE GALLBLADDER AND ACUTE PANCREATITIS

Age Group	*Without Pancreatitis* *Male*	*Per Cent*	*Female*	*Per Cent*	*With Pancreatitis* *Male*	*Per Cent*		*Female*	*Per Cent*	
0 10 yrs			1	0 4						
11 20 yrs										
21 30 yrs			2	0 7				1	3 2	(33 3)
31 40 yrs	4	2 1	7	2 5						
41 50 yrs	19	9 8	29	10 5	4	22 2	(17 4)	6	19 4	(17 1)
51 60 yrs	48	24 7	67	24 4	3	16 7	(5 9)	4	12 9	(5 6)
61 70 yrs	65	33 5	68	32 0	4	22 2	(6 2)	5	16 1	(4 3)
71 80 yrs	46	23 7	52	18 9	4	22 2	(8 0)	10	32 3	(16 1)
81 +	12	6 2	29	10 5	3	16 7	(20 0)	5	16 1	(14 7)
Total	194	9 7	275	18 2	18	19 4	(6 1)	31	45 6**	(13 8)

Per cent of autopsy population without pancreatitis in corresponding sex group
Per cent of autopsy population with pancreatitis in corresponding sex group
Figures in parenthesis represent per cent of all cases of inflammatory gallbladder disease in corresponding decade and sex and in bottom horizontal column per cent of total cases of corresponding sex with inflammatory disease of the gallbladder

Such statistical differences while they appear striking nevertheless raise some questions Despite the marked predominance of females showing chronic gallbladder disease both with and without pancreatitis the latter disease is about equally distributed between the two sexes Furthermore the breakdown of chronic disease of the gallbladder by decades as shown in Table IV bears no distinct relation to the age distribution curve for acute pancreatitis shown in Table II If acute pancreatitis can be caused by lymphatic drainage of infected material from the gall bladder then it appears reasonable to anticipate that the association of acute cholecystitis and acute pancreatitis would occur

most proponents favored entrance through the duodenal opening of the duct of Santorini. Several workers emphasized duodenal stasis as a cause of regurgitation into this duct. Illava showed that the intraductal injection of artificial gastric juice or bacteria into the pancreas resulted in hyperemia and fat necrosis of the pancreas and Carnot produced similar lesions by the intraductal injection of papain as well as diphtheria toxin. Others showed that a variety of corrosive substance could produce the same effect. With the discovery of enterokinase it was suggested that if intestinal juice could find its way into the pancreas autodigestion might occur but the experimental application of this idea met with failure and in the dog it was not even possible to force colored liquids from the intestine into the bile or pancreatic ducts. Thus considerations of regurgitation which were covered in the reviews by Opie and later by Dragstedt *et al.* have largely disappeared from present day reports at least insofar as infectious processes are concerned.

On a clinical level there are two possible relations between gastric or duodenal ulcer and acute pancreatitis. Those ulcers which are posterior may extend by direct continuity into the pancreas and the effect on the latter organ may derive from primary digestion by activated enzymes and secondary infection by bacteria present in the ulcer. On the other hand ulcers in other locations may produce a local dyskinesia of the stomach and duodenum which may conceivably lead to regurgitation of similar materials into the pancreatic ductal system.

TABLE VI

Gastric and Duodenal Ulcers and Acute Pancreatitis

	Without Pancreatitis				*With Pancreatitis*					
Age Group	*Male*	*Per Cent*	*Female*	*Per Cent*	*Male*	*Per Cent*		*Female*	*Per Cent*	
0-10 yrs	1	1.2								
11-20 yrs										
21-30 yrs										
31-40 yrs	3	3.6	2	5.3	1	50.0	(25.0)			
41-50 yrs	7	8.3	4	10.5	2	10.0	(22.2)	1	16.7	(20.0)
51-60 yrs	17	20.3	8	21.1	3	15.0	(15.0)	1	16.7	(11.1)
61-70 yrs	37	44.0	15	39.5	8	40.0	(17.8)	2	33.3	(11.8)
71-80 yrs	14	16.7	6	15.8	6	30.0	(30.0)	2	33.3	(25.0)
81 +	5	6.0	3	7.9						
Total	84	4.2	38	2.5	20	21.3	(19.2)	6	8.7	(13.0)

factors as infectious hepatic and gallbladder disease act indirectly in that the inflammatory exudate extends to the sphincter of the common duct and ampulla of Vater by direct tissue spread or in the bile producing a stenosis of these structures with resulting obstructive disease is presented in the section dealing with the latter

c) ***Direct Tissue Spread from Duodenal Ulcer, Duodenitis, Peritonitis or Infection of the Common Bile Duct or Ampulla of Vater*** Opie recognized the possibility that in certain cases of pancreatitis the disease may result from an ascending infection by way of the pancreatic ducts He cited Flexner Welch Cutler Reynolds and Moore Leonhardt Jackson and Ernst Ponfick and Marx Korte and also Carnot as having produced pancreatic abscesses in animals by the injection of bacteria into the pancreatic ducts Such organisms as E coli pneumonococci staphylococci diplococci Friedlander bacillus and others were utilized It was also recognized however that in many clinical cases admittance of bacteria to the pancreas was gained probably by secondary infection of obstructed ducts this aspect of the subject has been particularly studied in more recent years by Lewison and by Paxton and Payne On an experimental level bacteria have been seen in the pancreatic ducts of dogs with pancreatic fistulae but without pancreatitis However when glycosuria was present in addition acute edematous pancreatitis occurred E Coli and streptococci have been isolated from such lesions Nordmann has produced the experimental reflux of bile into the pancreas but pancreatitis has resulted only when the bile was deliberately infected

The validity of the concept of ascending infection into the pancreatic ducts is dependent in part upon a demonstration of the reflux of duodenal content into the pancreatic ductal system This idea appears to stem from the early observations of Fitz that acute pancreatitis occurs most frequently in individuals who have had attacks of gastric or gastroduodenal dyspepsia Subsequently the theory was developed that acute pancreatitis might be due to the reflux of gastric or duodenal content into the pancreas either via the duct of Wirsung or the duct of Santorini since it was pointed out that the latter is devoid of a sphincter

Infected omphalocele in a newborn male	1
Post operation for congenital volvulus in a 2 weeks old male infant	1

Gallbladder disease (cholelithiasis) was present in only four of these cases all with duodenal ulcers and in one of the latter gallstones were also found in the common duct Diabetes was present in one patient These cases are presented as possible examples of tissue spread from a peritonitis with certain reservations discussed below

d) *Activation of Bacteria Normally Present in the Pancreas* This is largely hypothetical although Illyia cultured bacteria from the pancreas of patients with acute pancreatitis However bacteria can also be cultured from the normal pancreas These may be saprophytic organisms since Siler *et al* believe that as a secondary event suppuration may begin a day or two following the onset of acute pancreatitis but usually is first noted after five to seven days or more

While the precise role of bacteria in the pathogenesis of acute pancreatitis has not been elucidated it appears that a significant proportion of cases with this disease show positive bacteriologic cultures Thus Schmieden and Sebening report 103 positive cultures of peritoneal fluid in acute pancreatitis and 84 negative ones 54 positive cultures of bile and 40 negative ones The organisms found were E coli staphylococci and streptococci Koller has described two fatal cases of interstitial pancreatitis provoked by the ingestion of codfish infected with hemolytic streptococci the organisms were cultured from the pancreas and peritoneal fluid and were also demonstrated histologically in the pancreas Thal and Molestina have been able to demonstrate organisms histologically in the pancreas in 6 of 31 fatal cases of acute hemorrhagic pancreatitis Veghelyi and coworkers have observed parenchymatous necrosis in the pancreas of infants dying of dysentery and infantile diarrhea but emphasize the role of toxins rather than direct bacterial action in the pathogenesis of the pancreatic lesion

It is evident from these experimental and statistical observa

	Number	Per Cent	Perforated	Per Cent	Number	Per Cent	Perforated	Per Cent
Male Gastric	42	2 1	4	0 2	9	9 6	1	1 1
Male Duodenal	42	2 1	13	0 7	11	11 7	4	4 3
Female Gastric	19	1 3	3	0 2	3	4 3	1	1 4
Female Duodenal	19	1 3	8	0 5	5	7 2		

Per cent of autopsy population without pancreatitis in corresponding sex group
Per cent of autopsy population with pancreatitis in corresponding sex group
Figures in parenthesis represent per cent of all ulcer cases in corresponding decade and sex and in bottom horizontal column per cent of total cases of corresponding sex with gastric or duodenal ulcers

Because of such considerations we have studied the statistical relations between acute pancreatitis and gastric and duodenal ulcers as shown in Table VI These ulcers were found about five times more frequently in cases of acute pancreatitis than in the general autopsy population and this relationship holds in both sexes despite the greater frequency of such ulcers in the male In the latter sex the age distribution curve parallels that shown in Table II for all cases of acute pancreatitis but in the female there were too few ulcer cases to warrant such a comparison The location i e whether gastric or duodenal appeared to have no influence on this relationship nor did the factor of perforation appear to increase the frequency of association with pancreatitis to a significant degree

Twenty of the 32 cases of acute pancreatitis presumed to be on an infectious basis were all associated with a generalized peritonitis connected with the following clinical incidents and distributed as shown

✓ Postappendectomy	1
Posthysterectomy	3
Postgastric surgery with intact suture lines	2
Postgastric surgery with disruption of duodenal stump or formation of duodenal fistula	4
Perforated duodenal ulcer	4
Perforated gastric ulcer	2
Perforated carcinoma of the colon	1
Ulcerative colitis with fistula formation	1

category However a word of caution is in order Irregularities in peristalsis and paralytic ileus are rather common complications of peritonitis and were present in some of these cases In such situations the reflux of bile and enzymic containing material from the upper intestinal tract cannot be excluded

tions that an infectious acute pancreatitis can occur in the absence of biliary tract disease and this is most clearly shown by those cases which develop as a complication of a bacteremia septicemia or viremia On the other hand the possibility exists that bacterial infection of the pancreatic ducts does not occur in the absence of obstruction of the pancreatic ducts It is difficult to assess the role played by each factor when such dual mechanisms exist Mayo Robson and also Nordmann have emphasized the fact that stasis of pancreatic juice within ducts dilated by obstruction by any cause would be followed shortly by the proliferation of bacteria in the stagnant secretion and Dragstedt *et al* point out that bacteria grow readily in pancreatic juice An analogy may perhaps be drawn with the urinary tract where stasis commonly leads to secondary infection but where the latter can occur even in the absence of obstruction to the urinary outflow Static pancreatic secretion may itself produce pancreatitis and in such an event saprophytic organisms resident in the pancreas may act only as secondary invaders as pointed out by Siler *et al* In cases of peritonitis secondary to surgical procedures on the stomach traumatic effects on the pancreas may also come into play and in penetrating or perforating ulcers as well as with disruption of the duodenal stump or the formation of duodenal fistulae the effect on the pancreas and peritoneal tissues may be primarily chemical due to bile and enzymic activators and again bacteria may act in only a secondary role

The significance of the increased frequency of inflammatory gallbladder and liver disease as regards an infectious etiology in acute pancreatitis remains in doubt Here too we may be dealing with a combination of factors perhaps metabolic as well as infectious With gastric and duodenal ulcers as pointed out enzymically activated fluids as well as infectious material may be regurgitated into the pancreatic ductal system

Nevertheless certain cases of peritonitis in the present series suggest a primary bacterial role in certain situations without the supervention of either intestinal secretion or trauma The cases of peritonitis following appendectomy and hysterectomy as well as those following perforation of a carcinoma of the colon or the formation of fistulae with ulcerative colitis appear to fall into this

salts the injection of sodium taurocolate was as effective as bile but the alcohol insoluble fraction of bile was ineffective

TABLE VII

THE ANATOMIC RELATION BETWEEN THE PANCREATIC AND COMMON BILE DUCT IN MAN (AFTER IVY AND GIBBS)

Author	*Total Number of Cases*	*Ducts open separately* *Number of Cases*	*Per Cent*	*Common Ampulla* *Number of Cases*	*Per Cent*	*Pancreatic Duct open 2-3 mm or more above Papilla permitting reflux* *Number of Cases*	*Per Cent*
			Anatomical Dissection				
Opie	100	11	11	89	89	28	28
Mann & Giordano	192	62	32	130	68	42	20
Baldwin	90	20	22	70	78	58	64
Belou	50	27	54	23	46	8	16
Rienhoff & Pickrell	246	73	29	173	71	81	32
Total	678	193	29	485	71	217	32
		Occlusion of Papillary Orifice and Injection of Bile Duct					
Millbourn	200	20	15			171	86
Hjorth	100	14	14			86	86
Cameron & Noble	100	26	26			66	66
Howard & Jones	150	41	27			81	54
Total	550	101	20			404	75
		Dissection Data Incomplete for Determining Potential Reflux					
Mehnen	449	175	39	274	61		
Schirmer	47	22	47	25	53		
Ruge	43	11	25	32	75		
Total	539	208	39.1	331	61.7		
Grand Totals	1767	511	29	816	46	621	60.0

In 21 of 75 cases the pancreatic duct joined the common bile duct 2.5 mm proximal to the papilla

Chapter 3

OBSTRUCTIVE DISEASE OF THE BILIARY AND/OR PANCREATIC DUCTAL SYSTEMS

a) *Stone Low in the Ampulla of Vater (Common Channel Theory)* Probably Opie's most important contribution to an understanding of the etiology of acute pancreatitis was his introduction of the Common Channel Theory. This is the oldest theory and was initially derived from attempts by Claude Bernard (1855) to induce acute pancreatitis in dogs by injecting bile mixed with sweet oil into the pancreatic ducts. The formal presentation of the idea that this disease is due to a reflux of bile into the pancreatic duct should however be credited to Lancereaux (1899). The association of pancreatic disease with alterations in the biliary passages in human cases was made by Korte, Oser, Opie and others. Opie first demonstrated that a temporary or permanent impaction of a stone into the ampulla of Vater in individuals in whom the common bile duct and duct of Wirsung unite to empty through this structure could induce pancreatitis and from such observations the Common Channel Theory was derived.

From Opie's earlier review it was evident that he as well as Day, Cutler, Kennan, Simpson, Chiari, Smith, Ehrich, Fraenkel, Korte, Moriani, Rolleston, Grawitz, Bryant and Lund had all reported cases showing that a small stone was required in order to obtain a reflux of bile into the pancreas. A large stone would act not only to obstruct the ampulla but also the mouths of the two ducts entering into it so that a reflux of bile would become impossible.

Opie also demonstrated that the injection of bile into the pancreatic duct of dogs resulted in typical acute hemorrhagic pancreatitis including inflammatory reaction and fat necrosis. Flexner as well as Pearce, Hewlett and Gulecke and in recent years Archibald, Baxter *et al.* and Popper have confirmed this observation. Flexner showed that the disease is produced by bile

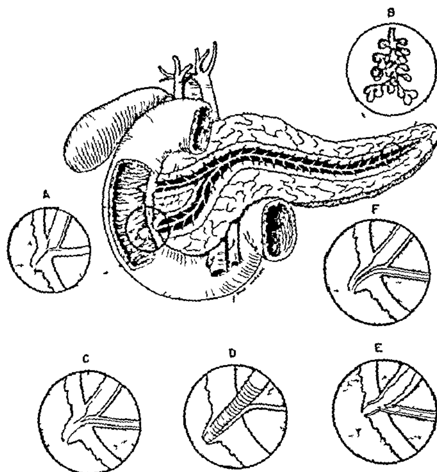


FIGURE 1

FIGURE 1 The common variations in the entrance of the Common Bile Duct and Duct of Wirsung into the duodenum These fall into 4 groups (1) Both ducts empty into the duodenum separately contiguous to each other or at separate points as shown at *F* (2) Both ducts are contiguous and their extreme ends open into a shallow ampulla as shown at *A* (3) Both ducts empty into a common deep ampulla of variable width as shown at C and E (4) The duct of Wirsung is markedly atrophic as shown at *D* consists only of a fibrous cord or is absent (From Hinton J W The recent advances in the management of pancreatitis Acute and chronic *Bull NY Acad Med* 28 425 1952)

On the other hand Sterling (1954) has made a rather detailed study of certain anatomic considerations in relation to the Com

Incidence of Visualization of Pancreatic Duct During Cholangiography

Author	*Number of Patients*	*Number Visualized*	*Per Cent Visualized*
Hunt Hicken Best	56	5	9
Robins & Hermanson	25	4	16
Colp & Doubilet	35	7	20
Leven	91	24	26
Howell & Bergh	64	27	42
Hjorth	430	202	47
Liedberg	53	22	41
Millbourn	181	72	40
Rudstrom	329	110	33
Hulten	110	26	24
Stenstrom	57	4	7
Total	1431	503	35

The extent to which the Common Channel Theory can be applied rests in the first instance, upon the frequency of occurrence of the anatomical situation which would make possible a reflux of bile into the pancreatic duct Not only must a common channel be anatomically demonstrable but the opening of the pancreatic duct must be 2 3 mm or more above the papilla to permit the impaction of a small stone without occluding the orifice of the duct of Wirsung A summary of such studies by various investigators is shown in Table VII from the review of Ivy and Gibbs Anatomically the presence of such a small stone could cause the reflux of bile into the pancreatic duct in from 16 to 64 per cent of cases (average 32 per cent) but edema of the papillary orifice or spasm of the sphincter of the lower ampulla could cause such reflux in from 46 to 89 per cent (average 71 per cent) If the papilla is occluded and the bile duct injected with a radio opaque material or a colored fluid possible reflex can be demonstrated in from 54 to 86 per cent (average 75 per cent) However during cholangiography the pancreatic duct may be visualized in only 7 to 47 per cent of cases (average 35 per cent) but Ivy and Gibbs point out that repeated attempts to visualize the pancreatic duct would undoubtedly increase the percentage so that it would approach the maximum possible percentage of about 70 per cent however they also state that the exact percentage possible will always remain moot, but it will certainly be higher than 30 per cent and less than 70 per cent

may be reversed with a reflux of pancreatic juice into the biliary tract as evidenced by the appearance of a high concentration of diastase in the bile of patients whose common bile ducts have been drained Normally, hepatic and gallbladder bile have only traces of diastase Hjorth later confirmed this observation and suggested that such a reflux of pancreatic juice may cause chronic cholecystitis with cholelithiasis and Gray Probstein and Sachar experimentally produced such chronic cholecystitis by causing a reflux of duodenal content with a high amylase concentration into the gallbladder Colp and coworkers have suggested that in some cases a reflux of pancreatic juice may cause acute cholecystitis Bottin attempted to induce acute hemorrhagic pancreatitis in dogs by producing an artificial common channel with obstruction although he failed to produce pancreatitis he found a mixture of bile and pancreatic juice in both ductal systems and in some animals an acute cholecystitis sometimes with perforation Schiller reported a case of acute hemorrhagic pancreatitis due to obstruction of the ampulla of Vater in which there were numerous foci of fat necrosis all over the parenchyma of the liver as well as in and about the pancreas He interpreted the hepatic foci as evidence for a reflux of pancreatic juice high in lipase content into the liver

In the dog if a strip of duodenum containing the mouth of the chief pancreatic duct is carefully anastomosed to the gall bladder and the accessory pancreatic duct is tied so that all of the activated pancreatic juice empties into the gallbladder no cholecystitis develops The latter is found only when significant tissue trauma accompanies the surgical procedure (Reid)

Still a third consideration is the communication between the primary and accessory ductal systems of the pancreas As Ivy and Gibbs have pointed out any pressure exerted through the duct of Wirsung in man could be equalized through its connection with the accessory duct of Santorini since the latter communicates with the intestine and with the chief duct of Wirsung Ivy and Gibbs have tabulated the data available on the percentage of persons in which this ductal communication could function The percentage in seven separate reports varied between 29 and 78

mon Channel in 59 specimens He has concluded that the termination of the common bile duct is transduodenal is at a papilla has a lumen which decreases in diameter like a funnel curves through a three dimensional route frequently intertwining with the pancreatic duct and unites with the latter to form an anatomic common channel in 55 to 60 per cent of cases he therefore raises an objection to the use of the term ampulla He has observed further that a common channel for the bile and pancreatic ducts which is less than one half of the transduodenal portion of the common bile duct does not readily permit intra ductal reflux because of the anatomic disposition of the sphincter and has determined that a functioning common channel to permit reflux may exist in only about 15 per cent of cases

A second prerequisite to the validity of this theory is that *the biliary pressure in the common duct is higher than the pan creatic secretory* pressure in the duct of Wirsung Mann and Giordano Herring and Simpson as well as Wangensteın Leven and Manson have reported that this is so but Wolfer as well as Harms have observed the reverse Ivy and Gibbs state that there is no good evidence showing that the secretory pressure of the bile and pancreatic juice is significantly different However as Dragstedt *et al* have reported respiratory movements vomiting and increased intra abdominal pressure may all increase the pres sure within the pancreatic ducts probably to a height equal to that in the common duct while according to Ivy and Gibbs the pressure in the common duct mav rise to as much as 100 cm of water under these circumstances In addition the gallbladder has the capacity to contract and exert a force on its content equal to about 25 cm of water and this may be added to the normal pressure within the common duct of about 30 cm of water On the other hand the capacity of the sphincter of Oddi or the in tramural portion of the common bile duct to offer resistance to the flow of fluid from the duct into the duodenum is 70 80 cm of water and it is known that reflux from the common duct into the pancreatic duct will occur at a pressure of 20 42 cm of water

Gray, Heifetz and Probstein have cited a fairly extensive literature showing that the flow in a common channel obstruction

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with an average of 44 per cent of 789 cases studied However the communication between the chief and accessory duct is sufficiently wide to permit a free communication in only about 15 per cent of persons

There are occasional anomalies in which the duct of Wirsung *is small and drains only the head of the pancreas whereas the* duct of Santorini is much larger and has a separate opening into the duodenum such cases have developed acute pancreatitis involving the whole gland There are also cases in which the duct of Wirsung and the common bile duct empty separately into the duodenum Johnstone (1907) reported four such cases with acute pancreatitis and Dardinski (1931) observed two others Popper *has found two and Rich and Duff also two No doubt* there are also more such instances which have not appeared in the literature

Some clinical reports substantiate the Common Channel Theory " while others fail to confirm it According to Dragstedt and coworkers cases supporting it have been reported by Thayer Opie Fuchs Bunting Deaver Rosenbach Guleke and Grant On the other hand Dragstedt *et al* point out that the occurrence of a stone in the ampulla without evidence of pancreatitis has been repeatedly observed at operation If a common channel exists in as high as 70 90 per cent of individuals and its obstruction were *the sole* necessary factor pancreatitis *would be ex*pected to occur more often in calculi of the common duct even if due consideration is given to the size of the stone as pointed out by Opie and others At best these observations indicate that the reflux of bile due to ampullary obstruction can account for only a small percentage of cases of acute pancreatitis While Dragstedt *et al* estimate that approximately 60 per cent of cases of acute pancreatitis arises in patients with antecedent chronic disease of the biliary tract, actual demonstration that an obstructed common channel has been operative can be shown in only about 10 per cent Schmieden and Sebening were able to find a *gallstone in the ampulla* in only 4 4 per cent of over 1200 cases of acute hemorrhagic pancreatitis and other workers (Fallis and Plain McWhorter and Lewison) in only nine of 125 patients (7 2 per cent) with this disease

TABLE VIII

OBSTRUCTIVE DISEASE OF THE COMMON DUCT AND ACUTE PANCREATITIS

	Without Pancreatitis				*With Pancreatitis*					
Age Group	*Male*	*Per Cent*	*Female*	*Per Cent*	*Male*	*Per Cent*		*Female*	*Per Cent*	
0-10 yrs	1	2 3	1	2 9						
11 20 yrs										
21-30 yrs	1	2 3								
31-40 yrs	3	6 8	4	11 4						
41-50 yrs	6	13 6	4	11 4	3	33 3	(33 3)	3	42 9	(42 9)
51 60 yrs	8	18 2	8	22 9	2	22 2	(20 0)			
61 70 yrs	14	31 8	13	37 1	2	22 2	(12 5)			
71-80 yrs	9	20 5	1	2 9	1	11 1	(10 0)	2	28 6	(66 7)
81 +	2	4 5	4	11 4	1	11 1	(33 3)	2	28 6	(33 3)
Total	44	2 2	35	2 3	9	9 6	(17 0)	7	10 1	(16 7)

Per cent of autopsy population without pancreatitis in corresponding sex group

Per cent of autopsy population with pancreatitis in corresponding sex group

Figures in parenthesis represent per cent of all cases of obstructive disease of the common duct in corresponding decade and sex and in bottom horizontal column per cent of total cases of corresponding sex with obstructive common duct disease

Furthermore it is evident from the cholangiographic studies noted previously which showed a regurgitation of radio opaque material as frequently as 40-47 per cent in some series that the reflux of bile into the pancreatic duct occurs with considerably greater frequency than acute pancreatitis Such a conclusion is also supported by certain data obtained in the present study Of a total of 27 cases showing choledocholithiasis to which the Common Channel principle might be applied only ten (37 per cent) showed acute pancreatitis The data obtained with all types of obstructive disease of the common duct demonstrable at autopsy are shown in Table VIII While such common duct obstruction was found in association with acute pancreatitis 4 4 times more often than in cases without pancreatitis of a total of 95 cases with obstructive disease of the common duct only 16 cases (16 8 per cent) developed acute pancreatitis In certain age groups the frequency of the latter association was much higher (33 3 to 66 7 per cent) but the number of cases in each age group was so small as to cast doubt on the significance of these figures

b) *Spasm or Edema of the Sphincter Oddi* Doubilet and Colp have reviewed the literature dealing with factors which

influence the action of the sphincter of Oddi They point out that animal investigations have shown that the resistance of the sphincter is greatly modified by various conditions such as the irritation of the gastric mucosa the distention of the stomach starvation local irritation of the sphincter by acid and stimulation by the autonomic nervous system The sphincter is relaxed through action of sympathetic system and is thrown into spasm by the parasympathetic innervation Since the nervous control of the sphincter is very complex these results are often inconstant Certain drugs will increase the tonicity of the sphincter by direct action on its muscle while others will reduce the tonicity and produce relaxation In addition the action of the duodenal musculature which surrounds the common bile duct as it obliquely penetrates the wall may also influence the resistance of the sphincter of Oddi

The suggestion by Dragstedt *et al* Archibald and others that edema or spasm of the sphincter of Oddi may act in the same manner as an obstruction by a calculus has received considerable attention in recent years The anatomical considerations upon which such a concept depends have already been mentioned however Mann and Giordano showed that many of the fibers of the sphincter surround the duct of Wirsung as well as the common duct so that by spasm the sphincter would close both the common bile and pancreatic ducts thus making regurgitation of bile into the pancreas impossible even though the spatial relations were proper

This theory has also found support in the demonstration by lipiodal studies that regurgitation into the duct of Wirsung is rather common But its strongest support probably derives from the observations by Doubilet and Mulholland that relief of recurrent upper abdominal pain associated with increases in serum amylase can be obtained in cases without evidence of an impacted stone by cutting the sphincter of Oddi

As Wapshaw has pointed out the evidence that gallbladder disease is an etiologic factor in acute pancreatitis is largely circumstantial The increased frequency of gallbladder disease in acute pancreatitis is often interpreted as support for a relation

ship between the two diseases. Such statistical data are generally applied in three ways: (1) In support of the idea that gallbladder stones may pass down the common duct and lodge temporarily in the ampulla of Vater to produce transient obstruction and initiate acute pancreatitis, or as already pointed out (2) infection originating in the gallbladder may extend down the common duct to produce inflammation, edema and spasm of the ampulla and as postulated by Richman (3) spasm of these structures may be initiated by a diseased gallbladder through a vagovagal reflex since the gallbladder and pancreas are innervated by the vagus nerves. Still a fourth mechanism has been suggested by Balo and Ballon: they believe that infection of the biliary tract may result in the production of mucus which might then plug the ampulla.

c) ***Duodenal Diverticula and Other Anomalies.*** Ogilvie has described three cases of acute pancreatitis accompanied by periVaterian duodenal diverticula. These patients had obstructive jaundice and he assumed that inflammation and swelling of such diverticula could produce obstruction of the ampulla with reflux of bile into the pancreas. Bockus estimates that about 5 per cent of patients over 55 have duodenal diverticula but we have been unable to find information on the frequency of location of this anomaly in the region of the ampulla of Vater. Duodenal diverticula were found in two of the 163 patients with acute pancreatitis in the present series but these were not located in the ampullary region and probably played no etiologic role.

Hughes has reported a case of acute pancreatitis in which obstruction of the pancreatic ductal system resulted from an anomalous location of the common bile duct. The common duct had a separate opening into the duodenum and had compressed the duct of Santorini while the duct of Wirsung was occluded by two stones.

d) *Spasm or Edema of the Sphincter or Papilla of the Pancreatic Duct.* Much of what has been discussed in the previous section regarding the sphincter of Oddi, the ampulla of Vater and the common bile duct also pertains to the duct of Wirsung, including considerations of communication between the latter

and the duct of Santorini Significant elevations in serum amylase indicative of pancreatic duct obstruction can be produced by the injection of morphine mecholyl pilocarpine or urocholine which produce contraction of the sphincter of the duct of Wirsung followed by the intravenous injection of secretin (Lagerlof Burke *et al* Myhre and coworkers as cited by Ivy and Gibbs) Structural considerations relative to this concept have been discussed in Chapter XIII

In a number of studies the morphological effects on the pancreas of stimulation of the vagus nerves have been described Babkin and coworkers noted a degranulation of acinar cells and the production of a juice rich in ferments and albumin with stronger vagal stimulation the acinar cells are almost completely depleted and the ducts filled with secretion Ramsay *et al* have found that peptone in the intestine stimulates pancreatic secretion through a nervous mechanism dependent on the integrity of the vagus nerve Howell and other physiologists state that reduced volume increased viscosity and a high enzymatic and protein content of the pancreatic secretions result from a vagal sympathetic stimulation or by inhibition of secretin activity In addition it appears that nervous mechanisms may also produce effects on the pancreatic ductal system for parasympathomimetic drugs cause not only the secretion of a viscid enzyme rich pancreatic juice but also a vasodilatation and probably a contraction of the sphincter of the pancreatic duct

Aside from the mechanics of obstruction of the pancreatic duct there remains the question as to whether or not acute pancreatitis can result from obstruction of the pancreatic duct alone, without the reflux of bile As a result of some of his experiments Opie (1901) realized that obstruction of the pancreatic duct alone could lead to acute pancreatitis but of lesser severity than that produced by bile injection Popper and Necheles observed only edema following partial ligation of the pancreatic ducts in dogs and the administration of secretin but when the pancreaticoduodenal artery was obstructed in addition hemorrhage and necrosis ensued Recent studies by Menguy *et al* have given essentially similar results although the latter used stimulation of the left splanchnic nerve to induce secretory activity in the pan

creas Thus obstruction of the pancreatic ducts must be accompanied by increased secretory activity of the gland to produce significant inflammatory change in the pancreas and by impairment of the circulation to produce a severe lesion

e) *Ascarides* Ivy and Gibbs have cited Schmieden as having found ascaris in the pancreatic duct in autopsies on 50 patients who died of acute pancreatitis The worm evidently caused obstruction and irritation of the pancreatic duct Duncan described a fatal case of acute pancreatic necrosis with abscess formation in an infant 18 months old the abscess cavity contained the remains of an adult ascaris and the stools contained ascaris Despite the relatively large series by Schmieden this must be considered a relatively rare etiology of acute pancreatitis

f) *Tumor or Calculi Obstructing the Pancreatic Duct* Surprisingly little has been reported as regards the association of pancreatic tumors with acute pancreatitis According to Richman acute pancreatitis is rare among patients who have undergone surgery for carcinoma of the pancreas either at the time of surgery or after the ducts have been ligated and sutured to the intestinal wall However Auger has pointed out that certain primary tumors of the pancreas are associated with fat necrosis in the pancreas omentum and mesentery and has cited similar cases reported by others He points out that such tumors show evidence of secretory activity even in metastatic sites and the tumor cells contain zymogen granules presumably necrosis of tumor cells releases pancreatic enzymes and produces fat necrosis Titone has reported a case of a man age 56 with a primary carcinoma of the pancreas with unusually widespread fat necrosis not only in the pancreas peripancreatic fat and mesentery but also in the retroperitoneal and subcutaneous fat especially of the arms and thighs no tumor cells could be found in or near the areas of necrosis and presumably this represented an instance of tumor secreting pancreatic enzymes into the blood or lymph stream

In contrast to ligation of the pancreatic ducts obstruction by carcinoma is generally insidious Barron has reviewed the litera

ture on the effects of carcinoma in the pancreas on its structural components and indicates that such obstruction leads primarily to atrophy with some regenerative hyperplasia of ducts and Kodama has observed the formation of retention cysts under such conditions Haunz and Baggenstoss point out that rupture of ducts with carcinoma of the pancreas is rare but dilatation of acini with rupture and fat necrosis is occasionally found On the other hand Puestow *et al* have reported a case of ampullary carcinoma which caused obstruction of the pancreatic ducts and acute hemorrhagic pancreatitis

In the present group of 24 cases of acute pancreatitis associated with obstruction of either the common bile or pancreatic ducts 14 were due to malignant tumors In one of these a 57 year old male there was a carcinoma originating in the common bile duct and extending into the duct of Wirsung to obstruct the latter A second case in a 72 year old female was of a carcinoma of the gallbladder which by extension also occluded the duct of Wirsung In still a third case in a 46 year old male the primary carcinoma was in the stomach but direct extension of the tumor had produced a compression of the distal end of the common duct A fourth case showed a primary carcinoma of the head of the pancreas also with compression of the terminal common bile duct In three other cases ranging in age between 46 and 50 years (2 males and 1 female) a malignant tumor of the duodenum had obliterated the vaterian orifice producing a Common Channel occlusion two of these were carcinomas and the third a lymphosarcoma The remaining seven cases ranging in age from 30 to 65 years (4 males and 3 females) all contained metastatic tumor in the pancreas with intrapancreatic compression of ducts in three of these the primary tumor was bronchiogenic in two a malignant melanoma and in the remaining two a carcinoma of the breast in females

However, even in our series the frequency of acute pancreatitis associated with pancreatic tumors is low The single primary carcinoma of the pancreas represents the only instance in 57 primary cancers of this organ (1 8 per cent) in which this association was found And the seven metastatic tumors with pancrea

titis represent 9 2 per cent of 76 cases in which the pancreas was the site of metastatic tumor

Unlike the situation with tumors of the pancreas much has been written on the significance of calculi in the pancreatic ducts but in most instances this has been in connection with so-called chronic relapsing or recurrent acute pancreatitis and in general it is not considered a common cause of an initial attack of acute pancreatitis Accordingly this aspect of the subject has been discussed in the chapters on sequelae of acute pancreatitis

g) *Epithelial Metaplasia in Pancreatic Ducts* Rich and Duff (1936) have been largely responsible for the idea that metaplasia of the epithelium of the pancreatic ducts may constitute a mechanism of obstruction of the latter and thus a cause of acute pancreatitis However Priesel (1922) and Balo and Ballon (1929) had previously described such metaplasia but without reference to inflammatory disease of the pancreas Rich and Duff found metaplastic foci obstructing pancreatic ducts in 13 of 24 cases of acute pancreatitis but Clark found this in only 11 per cent In addition the former workers found nonobstructing metaplasia in 23 of their 24 cases of acute pancreatitis and in 28 per cent of 150 unselected autopsies of persons over 25 years of age who had died of causes other than pancreatitis Priesel had observed focal metaplasia in 10 per cent of his series Balo and Ballon in 9 per cent Yotuyanagi in 64 per cent and Wainwright in only 3 2 per cent of 2500 patients without pancreatitis

In the series of 81 cases with metaplasia reported by Wainwright 49 showed focal dilatation of ductules in 14 there were focal areas of fibrosis in 13 foci of fat necrosis and in 5 some degree of inflammatory reaction Acute hemorrhagic pancreatitis was found in only 5 cases It is difficult to evaluate the significance of these percentages since there may have been cases showing combinations of these lesions and the occurrence or absence of combinations is not mentioned In the present series of 163 cases of acute pancreatitis ductal metaplasia was found in 34 instances (20 9 per cent) No attempt was made to determine the incidence of this ductal alteration in the total autopsy population but in a group of 111 cases utilized for a study on arterio

sclerosis in the pancreas ductal metaplasia without pancreatitis was found in 19 (17 2 per cent) At any rate it is evident that there is a sizeable percentage of cases showing ductal metaplasia without pancreatitis so that this lesion probably represents a response to local irritation and thus in some instances at least may constitute in effect of pancreatitis rather than a cause Thus in Wainwright s series there were ten cases of gallstones which may have represented a causal factor of at least as much significance as the ductal metaplasia

h) *Surgical Ligation* Reference has already been made to the surprising absence of acute pancreatitis following ligation of the ducts in the removal of pancreatic tumors but Cattell and Warren have observed in the pancreas obstructive phenomena produced by surgical ligation One of our cases of fulminating pancreatitis followed the removal of a cystadenoma of the pancreas but in this case it was difficult to determine whether the pancreatitis was the result of ductal ligation or of trauma incident to surgery

To summarize the statistic and anatomic evidence therefore supports the contention that in at least a sizeable proportion of cases of acute pancreatitis obstruction of the ampulla of Vater or of the pancreatic duct may be an important etiologic factor The evidence is strongest in those cases in which there is a definitive anatomic demonstration of such obstruction by either a calculus tumor duodenal diverticulum ascaris or surgical ligation The evidence is largely circumstantial as regards obstruction by spasm or edema either on an inflammatory or neurogenic basis or by temporary impaction of a gallstone which has escaped from a diseased gallbladder One element of proof which might lend support to the latter contention namely transient jaundice appears to be lacking in the large majority of cases attributed to this mechanism The mechanism by which pancreatitis develops following such mechanical obstruction is largely biochemical in which several factors appear to be involved A mild pancreatitis can apparently result from retention of pancreatic juice alone particularly if there is active secretion along with pancreatic ductal obstruction and a more severe reaction when there is an

admixture of bile and pancreatic juice (These are largely metabolic-chemical factors and will therefore be discussed in greater detail in Chapter IV) For severe acute hemorrhagic pancreatitis vascular occlusion in addition appears necessary

In the present series 24 (14 7 per cent) of the cases of acute pancreatitis were considered to be on such an obstructive basis with 17 (10 4 per cent) due to occlusion of the ampulla of Vater and the remaining 7 (4 3 per cent) due to obstruction of pancreatic ducts The breakdown of these was as follows

Occlusion of ampulla of Vater		17
By choledocholith	10	
By extension of tumor		
from common duct	1	
from duodenum	3	
from stomach	1	
from gallbladder	1	
from pancreas	1	
Occlusion of pancreatic duct		7
By metastatic carcinoma	7	

Chapter 4

METABOLIC FACTORS

1) *Liver Disease.* Pollack and Gerber have stated that "Interstitial inflammation of the pancreas is almost universal in all forms of cirrhosis and is frequently present in acute or subacute yellow atrophy, but the presence of fat or parenchymatous necrosis appears not to have been described prior to their report." The frequency of acute pancreatitis in cases with viral hepatitis has already been discussed and presumably the acute yellow atrophy noted by Pollack and Gerber were cases of viral disease of the liver. These investigators found a frequency of pancreatic fat necrosis of about 25 per cent in 88 cases of liver disease which they divided into Laennec's cirrhosis, acute and subacute yellow atrophy, toxic cirrhosis and cholangiolitic cirrhosis. They found only one instance of pancreatic fat necrosis in 100 control autopsies from which primary disease of the pancreas had been excluded and presumably also primary disease of the liver.

Pollack and Gerber found that jaundice was not a factor since only three of the 88 cases exhibited this symptom. They also ob-

TABLE IX

HEPATIC JAUNDICE AND ACUTE PANCREATITIS

	Without Pancreatitis				With Pancreatitis					
Age Group	*Male*	*Per Cent*	*Female*	*Per Cent*	*Male*	*Per Cent*		*Female*	*Per Cent*	
0-10 yrs	1	1.0	3	4.7	1	5.9	(50.0)			
11-20 yrs	2	2.1								
21-30 yrs	3	3.1	3	4.7				1	5.3	(25.0)
31-40 yrs	9	9.3	8	12.5	2	11.8	(18.2)			
41-50 yrs	12	12.4	12	18.8	3	17.6	(20.0)	4	21.1	(25.0)
51-60 yrs	24	24.7	19	29.7	4	23.5	(14.3)	6	31.6	(24.0)
61-70 yrs	34	35.1	15	23.4	5	29.4	(12.8)	4	21.1	(21.1)
71-80 yrs	11	11.3			2	11.8	(15.4)	2	10.5	
81 +	1	1.0	4	6.3				2	10.5	(33.3)
Total	97	4.9	64	4.2	17	18.1		19	27.5	

Per cent of autopsy population without pancreatitis in corresponding sex group.
Per cent of autopsy population with pancreatitis in corresponding sex group.
Figures in parenthesis represent per cent of all cases of hepatic jaundice in corresponding decade and sex and in bottom horizontal column per cent of total cases of corresponding sex with hepatic jaundice.

served that the pancreatic lesions bore no relation to the degree of hepatic inflammation but were more frequent in instances of severe hepatic (hepatocellular) degeneration They believed that the disease of the liver and of the pancreas have some common basis

Percentagewise the frequency of association of acute pancreatitis with jaundice secondary to hepatic disease (Table IX) is comparable to that which was found by Pollack and Gerber although the frequency of the symptom of jaundice was considerably lower in their study The frequency in females is about 9 per cent higher than in males If all cases of hepatic disease other than cirrhosis are excluded (Table X) acute pancreatitis remains about two to two and a half times more frequent than in the general autopsy population and here there is no significant sex difference

TABLE X

Cirrhosis of the Liver and Acute Pancreatitis

Age Group	Without Pancreatitis Male	Per Cent	Female	Per Cent	With Pancreatitis Male	Per Cent		Female	Per Cent	
0-10 yrs	3	3 4								
11 20 yrs	1	1 1								
21-30 yrs	1	1 1	2	2 2						
31 40 yrs	2	2 3	7	7 8	1	9 1	(33 3)			
41 50 yrs	8	9 1	10	11 1	1	9 1	(11 1)	2	28 6	(16 7)
51 60 yrs	22	25 0	23	25 6	3	27 3	(1_ 0)	2	28 6	(8 0)
61 70 yrs	28	31 8	25	27 8	3	27 3	(9 7)	2	28 6	(7 4)
71 80 yrs	16	18 2	19	21 1	3	27 3	(15 8	1	14 3	(5 0)
81 +	7	8 0	4	4 5						
Total	88	4 4	90	6 0	11	11 7	(11 1)	7	10 1	(9 3)

Per cent of autopsy population without pancreatitis of corresponding sex
Per cent of autopsy population with pancreatiti of corresponding sex
Figures in parenthesis represent per cent of cases of cirrhosis in corresponding sex and decade and in bottom horizontal column per cent of total cases of corresponding sex without cirrhosis

The conclusion of Pollack and Gerber that the diseases of the liver and pancreas may have some common basis is particularly worthy of consideration since many nutritional and toxic agents appear to simultaneously affect both organs This will become increasingly evident in the discussion of disease states involving metabolic factors which follows although the basic problem remains unsolved A second consideration is suggested by the ob

servations of Lynch and coworkers that about two thirds of cases with alcoholic fatty or cirrhotic livers show fat emboli to the lungs and in ten cases of mixed hepatic lesions nine showed fat emboli to the brain These authors postulate that the fatty cysts described by Hartroft and associates in such liver lesions may rupture and discharge fat into the bile canaliculi and/or vascular channels and then disseminate Presumably such emboli might also lodge in the pancreas where like atheromatous emboli they might produce pancreatitis Still a third consideration with regard to the role of the liver in the etiology of acute pancreatitis particularly with regard to nutritional and toxic factors is that the liver is the principal organ for detoxicating noxious chemical agents and when this function is impaired such factors may then attain sufficient concentration to injure the pancreas

b) *Nutritional Factors* Certain types of dietary deficiency suggest that malnutrition may produce changes in the liver and pancreas which may perhaps increase susceptibility to acute pancreatitis In the pancreas these changes consist of acinar ectasia with inspissation of secretion cyst formation and fibrosis Gilbert and Gillman have described changes in rats fed a deficient diet consisting of corn pap and sour milk and Gillman and Gillman later pointed out the resemblance of these alterations to those seen in cystic fibrosis of the pancreas in children Diets low in protein and high in fat have been reported by Friedman and Friedman *to produce similar changes in the pancreas and by* Grossman *et al* and Lindsay and coworkers to produce fatty liver and acute pancreatitis According to Lindsay *et al* and Chaikoff *et al* these changes in the liver and pancreas are comparable to those seen in alcoholic patients

Popper has pointed out the peculiar susceptibility of the pancreas to protein deficiency perhaps because of a high protein requirement incident to synthesis of enzymes Farber and Popper have produced interstitial inflammation and necrosis of pancreatic acini and fat by feeding DL-ethionine to rats This substance apparently competes with methionine in protein synthesis so that the protein molecules which *incorporate the ethionine cannot be* utilized Alvizouri and Warren also produced pancreatic necrosis with the same metabolic analogue and observed that in the liver

there was fatty metamorphosis as well as acute and subacute cholangitis thus showing the concomitance of hepatic and pancreatic disease as noted above

Farber and Popper have suggested that undernutrition in man may play a role in disorders of the pancreas by interfering with enzyme synthesis and clinical support for this contention may be derived from cases of acute pancreatitis associated with chronic debilitating disease such as ulcerative colitis (Ball Baggenstoss and Bargen Warren and Sommers) and kwashiorkor (Trowell *et al*) the latter being primarily a disease of insufficiency of dietary protein

An older report by Hueper and Martin is also interesting in this regard These workers fed rats excessive quantities of L tyrosine and found extensive inflammatory degenerative and cirrhotic lesions of the pancreas as well as inflammatory lesions of the biliary tract They also observed diabetes which they believed to be secondary to the pancreatitis Hueper and Martin suggested that the mechanism is either an activation of proteolytic pancreatic enzymes by the tyrosine or a direct toxic action of the latter It is also possible however that the requirement for tyrosine containing protein of the liver and pancreas is low and that an excess of such protein to the exclusion of proteins containing more essential amino acids may in a sense constitute a dietary insufficiency

c) ***Toxic and Chemical Irritants*** The investigations of Thal and Molestina demonstrating the permeability of the pancreatic ducts to staphylococcal toxin and the direct proteolytic action of the latter on pancreatic tissue has already been mentioned Veghelyi and coworkers have demonstrated a similar effect with the toxin of Shigella paradysenteriae While these investigators make no mention of hepatic changes it should be pointed out that such toxins are also capable of producing hepatocellular degeneration It is also pertinent that Veghelyi *et al* were able to produce similar pancreatic lesions with carbon tetrachloride a chemical agent also well known for its ability to produce marked liver damage and cirrhosis Drinker *et al* and Ivy have found that repeated injection of zinc oxide can cause chronic pancreati

tis in cats and dogs but no mention is made either of a preceding acute phase or of associated hepatic lesions

Certain of the effects mentioned in connection with various other etiologic factors may be considered to be in the nature of chemical irritants Thus as Ivy and Gibbs point out the reflux of bile into the pancreatic duct is considered to have the effect of initiating pancreatitis by its irritating properties However this is based largely on the utilization of relatively large volumes which according to some investigators may cause rupture of ducts Similar volumes *of trypsin or other substances* will also cause pancreatitis The experiments of Nordmann Mann and Giordano Bisgard and Baker Wangensteen and coworkers and Tejerina Fotheringham show that the passage of bile into the pancreatic ducts under conditions of pressure comparable to the normal in vivo state does not result in pancreatitis Ivy and Gibbs conclude that there is no evidence showing that the presence of bile in the pancreatic ducts in the absence of rupture of the latter or temporary obstruction to the outflow of pancreatic juice will cause either a rise in serum amylase or pancreatitis There is reason to believe however that when bile along with pancreatic juice enters the interstitial tissues the irritating properties of bile salts facilitates the action of pancreatic enzymes on the irritated tissues

Opie and Dragstedt *et al* have reviewed the earliest work by such investigators as Hess Hewlett Guleke Eppinger Sailer *and Spence Trevor Flexner and Pearce and Thiroloix and later* work has been reported by Lattes and by Binet and Brocq on the effects of direct instillation of various chemical substances into the pancreatic ducts Pancreatic necrosis has been produced by this technique with olive oil sweet oil oleic acid hydrochloric acid nitric acid formaldehyde chromic acid zinc chloride calcium chloride and fatty acids and sodium soaps On the other hand glycerin starch emulsion agar paraffin blood and serum have failed to produce necrosis of the pancreas

d) *Alcoholism* Richman has rather thoroughly reviewed reports dealing with the effects of ethyl and methyl alcohol on the pancreas Friedreich *(1878) first called attention to the association* of alcoholism and pancreatic disease and Fitz mentioned

that many cases of acute pancreatitis were addicted to the abuse of alcohol It is interesting that in Halsted's case with an impacted stone in the common duct upon which Opie first based his Common Channel hypothesis there was a history of alcoholic addition Lefas Lando and Poggenpohl were also among the early workers who noted the association of pancreatic disease and alcoholism

Egdahl Symmons Maeme as well as Adams were among the first to recognize the role of alcohol as a precipitating factor Carter and Domazalski and Wedge suggested that alcoholics suffer from repeated mild attacks which may eventuate in chronic relapsing pancreatitis but Bockus *et al* have pointed out that alcoholic pancreatitis is a more severe disease with a greater incidence of complications

There have been a great many reports on the frequency of association of alcoholism and pancreatic disease McWhorter obtained a history of alcoholism in 11 per cent of cases of acute pancreatitis Myers and Keefer in 21 per cent Rich and Duff in 29 per cent Weiner and Tennant in 66 per cent Clark in 16 per cent Paxton and Payne in 18 per cent and Bockus and Raffensberger in 50 per cent Wiener and Tennant also found that 53 per cent of patients dying in acute alcoholism had acute pancreatitis and Clark found such an association in 42 per cent According to Weiner and Tennant 47 per cent of chronic alcoholics had lesions of chronic pancreatitis and Kirshbaum and Shur have reported that of 356 fatal cases of hepatic cirrhosis in persons with a history of alcoholism well marked pancreatic fibrosis was present in 36 per cent

In the present series there were six of the 163 cases of acute pancreatitis (0 6 per cent) in which a history of excessive alcoholic intake was obtained These were all placed in the metabolic group because of associated liver disease and they constituted 35 3 per cent of this group

Despite the fact that alcoholism even in the absence of disease of the biliary tract may be a direct cause of pancreatitis little is known of the mechanism by which this occurs Experiments in animals with alcohol have not been successful in reproducing the clinical disease Egdahl and also Carter have suggested gastro

tis in cats and dogs but no mention is made either of a preceding acute phase or of associated hepatic lesions

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struction on the basis of either spasm edema or inflammation However other studies suggest a nutritional basis since alcoholics often manifest protein and vitamin deficiencies (Grossman *et al* Gillman and Gillman Davies Veghelyi Farber and Popper Goldberg *et al*)

Bennett *et al* have reviewed studies on the effects of methyl alcohol These patients exhibited prolonged elevations in serum amylase levels and the pancreatic damage as judged from the cases which came to autopsy seemed to be secondary to vascular injury and hemorrhage But there was also a depression of bicarbonate production in those patients which may have interfered with enzyme activity Other cases have been reported by Keeney and Mellinkoff and by Burhans The latter found necrosis as the most striking feature which he attributed to a direct action of methyl alcohol on the pancreas

In evaluating these reports Ivy and Gibbs summed up the mechanisms as follows (1) Obstruction of pancreatic outflow due to duodenitis with resulting pancreatic edema (2) Vomiting which may cause rupture of the ducts and acute hemorrhagic pancreatitis (3) Dietary deficiency may make the pancreas more susceptible to the first two factors

e) *Diabetes* The development of permanent diabetes following attacks of acute and recurrent pancreatitis has been reported by Warren and LeCompte Sprague and also by Becker Transient hyperglycemia and glycosuria have been noted during attacks of acute pancreatitis by Shumacker and as previously noted patients have died with a combination of diabetic coma and fulminating acute pancreatitis (Rodrigues Steiner and Tracy Root)

Warfield (1927) considered the occurrence of hemorrhagic pancreatitis in diabetes a rarity and explained this by the fact that patients with diabetes live too short a period to develop such a complication Umber earlier had stated that diabetes can develop following acute pancreatitis only if there exists a congenital inferior insulin mechanism According to Joslin the diabetic patient is more subject to acute pancreatitis than the non diabetic Bossak and Joelson have recently reported eight cases all females of acute pancreatitis and diabetes in a series of 106 cases

enteritis is a responsible factor and Myers and Keefer have postulated that alcohol in the blood may act directly on the pancreas on the duodenum where it may cause congestion or inflammation and with persistent vomiting there may be regurgitation of duodenal content into the pancreatic ducts Kuwschinski (1888) first showed that alcohol by *mouth in animals stimulated* the flow of pancreatic juice and Fleig (1903) observed a similar effect by placing alcohol in an isolated loop of small intestine Zitovich made a similar observation by the intraduodenal administration of alcohol Bayliss and Starling showed that alcohol can stimulate the formation of secretin by a direct action on the duodenal mucosa and Rich and Duff suggested that alcohol or food coming in contact with the duodenal mucosa could stimulate the flow of pancreatic juice and in the case of alcohol an associated duodenitis and inflammation of the papilla of Vater may produce a resistance to the outflow of excessive pancreatic juice

However Gizelt showed that the installation of alcohol into the isolated stomach or even in the rectum had the same effect and he believed that alcohol exerted a direct effect on the pancreas via the blood stream Newman and Mehrtens showed that intravenous alcohol was equally as effective and suggested that it might be through the elaboration of a histamine like substance that pancreatitis was produced

Richman has postulated that alcohol stimulates the secretion of hydrochloric acid and histamine the acid enters the duodenum and heightens secretin formation and the latter is also increased by a direct effect of alcohol on the duodenal mucosa The absorbed histamine may also act as a direct pancreatic stimulant via *the blood stream* as suggested by MacKay McGowan and coworkers have shown that hydrochloric acid and alcohol may cause spasm and edema of the sphincter of Oddi and Dreiling *et al* have suggested that the latter along with the heightened secretory activity as postulated by Richman may result in a large volume of pancreatic secretion acting against an ampullary obstruction such as suggested by Rich and Duff

Thus many observers feel that the mechanism by which acute pancreatitis is produced in alcoholism is a dual one with heightened pancreatic secretory activity coupled with ampullary ob

struction on the basis of either spasm edema or inflammation However other studies suggest a nutritional basis since alcoholics often manifest protein and vitamin deficiencies (Grossman *et al* Gillman and Gillman Davies Veghelyi Farber and Popper Goldberg *et al*)

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with disease of the pancreas Rose found seven diabetics in a series of 89 patients with acute pancreatitis and Bowers and Atkins three diabetics in 17 such cases Warren and LeCompte found 17 cases of pancreatitis in 811 autopsies on diabetic patients (2 1 per cent)

TABLE XI

DIABETES AND ACUTE PANCREATITIS

Age Group	*Without Pancreatitis* Male	Per Cent	Female	Per Cent	*With Pancreatitis* Male	Per Cent		Female	Per Cent	
0 10 yrs	1	0 8								
11 20 yrs			3	2 2						
21 30 yrs	1	0 8	2	1 5	1	8 3	(50 0)			
31-40 yrs	7	5 5	8	5 8	2	16 7	(22 2)			
41 50 yrs	7	5 5	12	8 8	2	16 7	(22 2)	2	20 0	(14 3)
51 60 yrs	36	28 1	31	22 6	1	8 3	(2 7)	1	10 0	(3 2)
61 70 yrs	50	39 1	49	35 8	3	25 0	(5 7)	5	50 0	(9 2)
71 80 yrs	*24*	*18 8*	*23*	*16 8*	*3*	*25 0*	*(11 1)*	*2*	*20 0*	*(8 0)*
80 +	2	1 6	9	6 6						
Total	128	6 4	137	9 1	12	12 8	(8 6)	10	13 0	(6 2)

Per cent of autopsy population without pancreatitis in corresponding sex group
Per cent of autopsy population with pancreatitis in corresponding sex group
Figures in parenthesis represent per cent of all cases of diabetes in corresponding decade and sex and in bottom horizontal column per cent of total cases of corresponding sex with diabetes

There was a total of 287 cases of diabetes in our total autopsy population in 22 of which acute pancreatitis was found (8 0 per cent) this was almost four times the frequency found by Warren and LeCompte Since there were 163 cases of acute pancreatitis these 22 diabetics constituted 13 5 per cent of the group with pancreatic disease The age and sex distribution is shown in Table XI where it can be seen that while the frequency of diabetes is slightly higher among females the incidence of complicating acute pancreatitis is about equal in the two sexes

The excessively high mortality in diabetic patients with acute pancreatitis appears to have been observed in many of these reports and cannot be correlated with the anatomic lesions which are not particularly severe *Fallis has made the statement that* when a diabetic patient is attacked by acute pancreatitis the diagnosis is grave indeed It is pertinent that in hemochromatosis in which there is an associated diabetes as well as certain tissue alterations in the pancreas consisting of fatty infiltration

and fibrosis with hemosiderin deposition in acini, ducts and islets which might conceivably render this organ more susceptible, there is no evidence of increased susceptibility to acute pancreatitis. In the eight cases with diabetes reported by Bossak and Joelson, alcoholism was present in one, biliary tract disease in one and hyperlipemia in two. Severe arteriosclerosis was present in only one. These investigators postulate that some lesion of the smaller arterioles or capillaries might be provocative or that ischemia due to vasospasm might be a cause. Morton has reported a case in which acute pancreatitis was associated with diabetes, hyperlipemia and xanthomatosis. The role of hyperlipemia in the pathogenesis of acute pancreatitis is discussed in the following section.

f) *Hyperlipemia.* In reporting a case of relapsing pancreatitis and hyperlipemia, Klatskin and Gordon have presented a rather thorough review of reports dealing with this association. They credit Speck (1846) with having described the first case and since then eleven others (including their case) have been reported, bringing the total to date to only twelve.

Klatskin and Gordon have pointed out that the pancreatitis in such cases is usually of the chronic relapsing variety (acute recurrent) and that the hyperlipemia is often not noted until several attacks have occurred, thus raising the question as to whether the hyperlipemia is causally related or a result of pancreatic disease. These cases typically show a marked increase in neutral fat, often with a concomitant but less marked rise in cholesterol and phospholipid. Occasionally the pancreatitis is accompanied by xanthomatosis of the skin of the eruptive type and by lipemia retinalis. Xanthomatosis has been observed before the onset of abdominal pain in some cases, thus suggesting that *the hyperlipemia may precede the development of pancreatitis.*

Most of the cases reported have occurred in early childhood or in early adult life and most of the authors have attributed the lipemia to an alteration in fat metabolism related to pancreatic insufficiency, based on the assumption that the pancreas exerts an hormonal control over lipid metabolism. However, Chaikoff and associates have shown that the lipotropic activity of the pancreas on the fatty liver is due to the presence in the pancreas

of an enzyme necessary for the absorption of bound methionine and choline in the diet and not to an hormonal effect as suggested by Dragstedt Furthermore since the serum lipid level falls following pancreatectomy in insulin treated dogs it appears unlikely that the lipemia is due to a pancreatic insufficiency

The only reports of serum lipid studies in animals with experimental pancreatitis are contradictory Binet and Brocq have observed transient increases in serum lipids but Marcus was unable to produce lipemia under similar conditions In recent experiments in which acute pancreatitis was produced by cortisone in rabbits Stumpf and associates have observed a hyperlipemia similar to that found in the case of Klatskin and Gordon incident to the administration of the hormone

Klatskin and Gordon have found certain striking similarities between their case of relapsing pancreatitis with hyperlipemia and idiopathic or essential familial hyperlipemia an idea supported by the report of Poulsen describing pancreatitis and hyperlipemia in two siblings Based on such evidence it would appear that the lipemia preceded the pancreatitis Additional support may be derived from the persistence of lipemia between attacks of pancreatitis and the observation of the appearance of xanthomas before the onset of abdominal symptoms On the other hand many of the abdominal crises seen in patients with essential familial hyperlipemia are not associated with elevations in serum or urine amylase and there is an absence of pancreatitis in the only such cases to be reported complete with autopsy

Klatskin and Gordon favor the idea that the pancreatitis is produced by fat emboli which lodge in pancreatic vessels based on a hypothesis suggested by Swank that embolization of the capillaries by clustered chylomicrons may lead to significant pathologic lesions In support of such a pathogenesis are the reports of fat embolism in diabetic and other types of hyperlipemia and the observation by Bantin of such emboli actually moving through the retinal vessels during life Furthermore in some cases of essential hyperlipemia and pancreatitis there have been clinical features to suggest embolic phenomena in other organs Fat emboli in cases of pancreatitis have been observed by Grondahl by Elting and Martin and by Warthin but Tourtel

lotte and Tyler were unable to demonstrate fat emboli in the pancreas lung heart liver and kidney in a case of acute pancreatitis associated with diabetes and hyperlipemia Furthermore Lynch has reported four cases of fat embolization with acute pancreatitis in which he considers this phenomenon a complication and cause of death rather than a cause of the pancreatic lesion since such emboli were found in the kidney associated with nephrosis which he considered a possible cause of death Lynch is also of the opinion that the focal cerebral and visceral lesions associated with pancreatitis which Vogel has ascribed to circulating enzymes may also be attributed to fat emboli The rise to hyperlipemic levels during the attack of pancreatitis and the subsequent fall to normal levels when the attack subsides is taken by some (Coffey) as evidence against hyperlipemia as an etiologic factor and in favor of it being a consequence of the disease

g) ***Hormonal Factors*** Acute pancreatitis has been produced in rabbits treated with cortisone by Stumpf *et al* and by Bencosme and Lazarus Since the latter workers found that neither vitamin supplementation of the diet nor the prophylactic administration of antibiotics influenced the development of pancreatic lesions it would appear unlikely that the latter developed on an infectious or dietary basis however alterations in protein metabolism have not been excluded a particularly important consideration since the acinar changes resembled those produced by Hueper and Martin by the excessive feeding of tyrosine It may be that altered protein metabolism brings about these changes in the acinar cells of the pancreas particularly since cortisone is known to depress protein synthesis

Hyperlipemia incident to cortisone administration is considered the principal pathogenic factor by Stumpf *et al* as mentioned previously but Bencosme and Lazarus have emphasized an obstructive etiology possibly caused by the cortisone induced increase in the viscosity of the secretory material Carone and Liebow have found acute pancreatitis in 16 of 54 patients treated for various diseases with cortisone and/or ACTH and like Bencosme and Lazarus give primary consideration to a direct steroid effect on the pancreatic acinar cells

Cortisone administration may have been a factor in two of our cases of acute pancreatitis In the first a 70 year old female there was a huge posterior ulcer penetrating into the pancreas and *the hormone may have been effective in advancing the circumference* and depth of the ulcer The second patient was a 74 year old male with severe cardiovascular disease from which he succumbed However he had been receiving cortisone for arthritis for a long period of time and had developed skin lesions a biopsy of which revealed an acute vasculitis which was attributed to cortisone therapy Healing vascular lesions of similar type *were found in the pancreas and the pancreatitis was considered* as probably being due to these vascular lesions

Cope and coworkers *have recently shown that hyperparathyroidism* may be manifested by pancreatitis without concomitant bone *disease urinary tract calcification or peptic* ulcer and without elevation of serum calcium They believe that parathyroid dysfunction may cause ductal obstruction and pancreatitis as a result of the formation of calculi in the pancreas and advise investigation of parathyroid function in all patients with pancreatitis Whether *there is such a causal relationship or* merely two concomitant disease processes remains to be evaluated by further study since pancreatitis has not been reported heretofore as a common finding even in cases of hyperparathyroidism with advanced bone lesions and urinary tract calcification

h) ***Pregnancy*** Pancreatitis occurring during or immediately after pregnancy has been reported and appears to be related in part at least to concomitant disease of the biliary tract or stasis within the biliary tree or duodenum Joske has reported six cases of acute pancreatitis following pregnancy four of whom required cholecystectomy one drainage of the biliary system and in the sixth *the process subsided spontaneously Cassel and Malewitz* have also reported a case of acute pancreatitis in pregnancy admitted to our hospital This woman was apparently free of biliary tract disease with a negative cholecystogram They believe that it should be expected that the incidence of pancreatitis would be increased during pregnancy because the pressure of the gravid … by direct or indirect means produce a blocking

mechanism on the biliary pancreatic ductal system Since this case recovered it is not included in the present series

Fitzgerald has studied pancreatic function in pregnancy and has found a decrease in enzyme secretion and he has related pancreatitis to a rebound from this state with an overproduction of enzymes Millen and coworkers have suggested hyperlipemia as a cause in pregnancy on the basis of one case showing elevated serum lipids and acute pancreatitis however it is doubtful if the hyperlipemia in this case was due to the pregnancy Since there are so few cases reported as occurring during pregnancy one wonders if the pancreatitis is only a concomitant disease with pregnancy exerting no causal relation

i) *Uremia* Wallace and Ashworth (1941) first reported dilatation of acini with retention of secretion in 45 5 per cent of 200 unselected autopsies there was an incidence of 56 per cent in patients over 50 years and 38 3 per cent in patients under 50 Subsequently Baggenstoss (1948) found that about 48 per cent of a series of 270 autopsies on uremic patients showed such acinar ectasia as compared with only 20 per cent in a control group the uremics were divided into those with chronic glomerulonephritis those with hypertension and nephrosclerosis and a miscellaneous group some with renal and others with extrarenal causes Menten and Kinsey found this acinar alteration in 13 7 per cent of 256 autopsies on patients dying with a variety of diseases and Stein and Powers in 21 per cent of 358 consecutive autopsies Warren and Sommers have reported essentially the same changes in 75 per cent of patients with ulcerative colitis as compared with 41 per cent of a control series and Ball Baggenstoss and Bargen found an incidence of 53 per cent in patients with this disease as compared with only 19 per cent in a control series

In the series of Menten and Kinsey and in a report by Baggenstoss Power and Grindlay there was a high incidence of pancreatic acinar ectasia in diseases affecting the gastrointestinal tract and it has therefore been linked causally with metabolic and/or nutritional disturbances Support for such a concept may also be derived from reports already cited on the relation of nutritional factors to acute pancreatitis However Baggenstoss believes that the latter is only one of a series of factors responsible

for this alteration and concludes that the following have to be considered

1 Inhibition of pancreatic secretion perhaps by a failure of the secretin stimulatory mechanism This recognizes the association with gastrointestinal disturbances

2 Nervous stimulation mediated through the vagus and parasympathetic nerves with resultant viscid pancreatic juice and retention of the latter

3 Dehydration contributing to the increased viscosity of the pancreatic juice This may be related both to the gastrointestinal disturbance and to certain types of renal uremia

4 Malnutrition (Protein Deficiency) This too may be related to both the factors mentioned in 3

TABLE XII

UREMIA AND PANCREATITIS

Age Group	*Without Pancreatitis* Male	Per Cent	Female	Per Cent	*With Pancreatitis* Male	Per Cent		Female	Per Cent	
0 10 yrs	2	3 4	1	1 9						
11 20 yrs	2	3 4								
21 30 yrs	4	6 8	2	3 8	1	5 0	(20 0)	2	13 3	(50 0)
31 40 yrs	5	8 5	8	15 1	3	15 0	(37 5)			
41 50 yrs	8	13 6	7	13 2	3	15 0	(27 3)	3	20 0	(30 0)
51 60 yrs	12	20 3	20	37 7	4	20 0	(25 0)	1	6 7	(4 8)
61 70 yrs	17	28 8	12	22 6	4	20 0	(19 0)	6	40 0	(33 3)
71 80 yrs	4	6 8	1	1 9	5	25 0	(55 6)	3	20 0	(75 0)
81 +	5	8 5	2	3 8						
Total	59	3 0	53	1 3	20	21 3	(25 3)	15	21 7	(2[illegible] 1)

Per cent of autopsy population without pancreatitis of corresponding sex

Per cent of autopsy population with pancreatitis of corresponding sex

Figures in parenthesis represent per cent of all cases of renal uremia in corresponding sex and decade and in bottom horizontal column per cent of total cases of corresponding sex with renal uremia

The lesion has been described as consisting first of interstitial edema infiltration of neutrophiles and inspissation of secretion followed by lymphocytic infiltration and fibrosis These changes may therefore be regarded as a mild form of acute pancreatitis although necrosis is not a feature of this lesion While such alterations in the pancreas do not progress beyond these stages in uremia and in various diseases of the gastrointestinal tract in which they were found it is conceivable that it creates a susceptibility of the pancreas so that a minimal additional insult might

result in overt acute pancreatitis Because of this consideration we have compared the frequency of uremia in the cases of pancreatitis with its incidence in the general autopsy population as shown in Table XII Surprisingly the frequency of uremia in males with acute pancreatitis is about seven times greater than in the general male autopsy population and in females this association is almost 17 times greater than in the total female autopsy population This is a greater difference than we have found with inflammatory disease of the gallbladder inflammatory disease of the liver gastric and duodenal ulcers obstructive disease of the common duct hepatic jaundice hepatic cirrhosis or diabetes in fact with all diseases which are believed to be causally related to acute pancreatitis Whether this increased susceptibility of the pancreas to acute inflammation of that organ is related to metabolic factors as postulated by Baggenstoss or whether it is related to the high incidence of pancreatic vascular disease in such patients is not known it is quite possible that all of these factors play an important role

Of the 18 cases in our series which have been considered to be primarily on a metabolic basis 6 were in alcoholics with either fatty or cirrhotic livers 5 were in cirrhotics without a history of alcoholism 3 were primary carcinomas of the liver two were patients who had received extensive cortisone therapy and 2 were infants in whom extensive uric acid deposits were found in the kidneys in one of which there was also marked hepatic fatty infiltration With regard to the latter it may be pertinent that Groen has observed a combination of fatty liver and similar renal disease in dogs by the exclusive feeding of bacon While this indicates some metabolic defect presumably affecting protein metabolism the true nature of this disease in newborn infants remains unknown In Table X we have shown 18 patients with cirrhosis of the liver and acute pancreatitis but have placed only 11 of these in the category of primary metabolic disease six of the remainder were instances of biliary cirrhosis secondary to common duct obstruction and have been included in the group of cases which developed acute pancreatitis on the basis of ampullary occlusion and the seventh was a case of postnecrotic cirrhosis considered as due to hepatitis virus

Chapter 5

TRAUMATIC FACTORS

Despite the fact that the pancreas occupies a deep and seem
ingly protected position in the abdomen its structure vascularity
and fragility are such that even minor trauma may result in
injury Becker has classified pancreatic injuries into three cate
gories (1) Operative (2) Penetrating and (3) Non penetrat
ing To these should be added another (4) Electric Shock Ac
cording to Becker the incidence of traumatic pancreatitis at the
Charity Hospital in New Orleans is 5 per cent of the cases of
acute pancreatitis

a) *Operative* Millbourn (1949) appears to have first ob-
served elevations in serum amylase in a large number of patients
subjected to gastrectomy for peptic ulcer and directed attention
to the development of clinical pancreatitis following such opera
tive procedures He believed that the pancreas was either trau
matized directly or the pancreatic duct injured in dissecting away
the ulcer Perryman and Hoerr found elevations in serum amylase
in 27 of 85 patients (46 per cent) undergoing surgery of the up
per gastrointestinal and biliary tracts they found a 35 per cent
incidence in common bile duct exploration and 33 per cent in
direct procedures on the pancreas and suggested that manipula
tion of the pancreas may produce a mild disease Brown has also
observed acute hemorrhagic pancreatitis following common duct
exploration

Warren drew attention to the fact that this highly lethal
complication may occur in some instances without injury to the
pancreas or its blood supply and in situations in which the reflux
of bile can be excluded However Cattell and Warren have noted
that the duct of Santorini is particularly vulnerable to surgical
injury and that the consequence of such injury depends on the
size of the duct the character of the injury (laceration division
or ligation) the type of sutures and the functional state of the

pancreas in the immediate postoperative period They also suggested duodenal stasis as a cause

Certain of the cases reported by Dunphy and coworkers indicate that interference with the blood supply to the pancreas may be important when combined with trauma or partial obstruction to the pancreatic ducts The posterior pancreatico duodenal artery and the duct of Santorini are particularly vulnerable to injury when the duodenum is mobilized during gastrectomy They suggest that when major obstruction to the ducts can be excluded sludging of pancreatic secretion incident to medication dehydration or other factors associated with surgical operations may be a factor Block *et al* have also pointed out the possibility that postoperative pancreatitis following abdominal surgery may be related to impairment of the circulation

b) *Penetrating Wounds* Penetrating wounds of the pancreas are relatively uncommon in civilian practice Such trauma is usually the result of bullets or knives In addition to hemorrhage rupture of the capsule with release and activation of enzymes combine to produce hemorrhagic pancreatitis A rather unusual case was reported by Robinson following translumbar aortography Since there was no evidence that the needle had touched the pancreas he assumed that an excessive concentration of dye had reached the coeliac axis and then continued through the pancreatic artery to the pancreas

c) *Non penetrating Trauma* Travers (1872) first reported rupture of the pancreas following a compression injury to the abdomen Stern (1931) later described eight additional cases and Keynes (1944) reported a case due to a blast from an under water explosion emphasizing that even a mild force may produce pancreatic damage and that other organs such as the duodenum and jejunum may be involved Other cases have been reported by Phillips and Seybold and by Coffey the latter by injuries from boxing night sticks automobile accidents or falls

As regards the non penetrating injuries to the epigastrium Venable has suggested that pancreatic rupture may be of two types (1) incomplete rupture in which the laceration involves only the parenchymal portion of the gland without capsular

disruption and (2) complete rupture in which both the capsule and the parenchyma are torn In either instance the pancreatic ducts may be ruptured or the external pancreatic secretion forced through the duct walls into the interstitial tissues the pancreas continues its active secretion and the extravasated pancreatic digestive ferments exert a necrotizing effect upon the blood vessels and parenchyma of the gland

d) *Electric Shock* As regards the fourth form of trauma to the pancreas Glazer has reported three cases of acute pancreatitis in soldiers accidentally electrocuted and Sirolli has observed extensive hemorrhage and necrosis in animals dying of electric shock

Nine of the 163 cases of acute pancreatitis in the present series (5 5 per cent) were attributed to trauma Three of these all females ranging in age between 61 and 74 years developed this complication following gastric surgery in two extensive venous thrombosis was found Four other cases two females and two males ranging in age from 58 to 74 years developed pancreatitis following upper abdominal surgery for carcinoma There was a single instance in a 61 year old female of fulminating pancreatitis following the resection of a pancreatic cyst The ninth case resulted from a blow to the epigastrium of a 59 year old male due to an automobile accident there was also rupture of the diaphragm with herniation of the stomach colon and spleen through this hiatus

Chapter 6

VASCULAR FACTORS

a) *Venous Stasis and Thrombosis* In general alterations in the venous side of the pancreatic circulation has received much less attention than changes in the arterial blood supply as a causal mechanism in acute pancreatitis Ivy and Gibbs have pointed out that venous stasis may be caused by edema of the gland or an increase in pressure in ducts due to obstruction and would predispose to congestion and thrombosis of veins A pressure in the ducts or within the capsule of the pancreas of as little as 20 25 cm of water somewhat less than the secretory pressure should cause some venous stasis Decreased blood flow would then predispose to venous congestion They thus suggest that such a process of venous stasis and thrombosis would result in a form of wet gangrene"

Von Glahn and Chobot in 1925 drew attention to the importance of the venous circulation of the pancreas when they described in detail for the first time the changes in the pancreas in cases of heart failure Among the distinctive features were areas of capillary congestion at the periphery of the primary lobules with atrophy of the parenchymal cells and condensation of the connective tissue framework in the congested areas There was no congestion of the islands of Langerhans which occupy a position analagous to the portal area in the liver Later Beck and Peterson reproduced these lesions in rats by increasing the pressure in the veins of the pancreas by partially obstructing the flow of blood through the inferior vena cava between the base of the heart and the diaphragm While such observations have not been related to acute pancreatitis they may have clinical significance in several respects Socalled terminal pancreatitis as reported by Burn and by Sachar and Probstein and related by them to circulatory failure could conceivably be due to venous stasis and perhaps even venous thrombosis Evidence of such thrombosis

will be presented subsequently Furthermore, since the primary venous drainage of the pancreas is into the portal vein venous congestion should be anticipated in cirrhosis of the liver While an increase in the incidence of pancreatitis in this hepatic disease is well recognized and is illustrated statistically in Table X it has generally been related to metabolic and toxic factors and the factor of venous congestion in pancreatitis associated with cirrhosis has never really been evaluated In addition capillary stasis and thrombosis have been reported by Ackerman as the result of a transfusion reaction in a case which also developed acute pancreatitis in addition this patient developed shock which probably contributed a factor of venous stasis One case of the latter type in a 62 year old female is also included in the present series of 22 cases of acute pancreatitis presumed to be on a vascular basis

b) *Arterial Occlusion* Panum (1862) appears to have first pointed out the possible importance of circulatory disturbances as an etiologic factor in acute pancreatitis He injected small particles of wax into the pancreatic arteries thus producing hemorrhage of the pancreas Lepine Bunge Guleke and others subsequently showed that simple ligation of arteries is without effect but the injection of lycopodium powder air petroleum and other foreign materials results in hemorrhagic infarcts Several investigators (Radakovich *et al* MacKenzie) have combined obstruction or ligation of the pancreatic duct and the injection of oil or paraffin into the pancreatic arteries to produce pancreatic necrosis A number of other workers have produced acute pancreatitis by a combination of ligation of pancreatic vessels and a variety of techniques which have produced mechanical damage to pancreatic tissue (Levin Langerhans Hildebrand Katz and Winkler Doberauer) this older work has been reviewed by Opie Smyth was able to produce focal acute pancreatic necrosis in dogs by the intra arterial injection of mercury but the process could not be intensified by the stimulation of secretion of pancreatic enzymes

Block Wakim and Baggenstoss have recently reported that obstruction of the pancreatic ducts in the rat produces only edema inflammation atrophy of acini and fat necrosis but the

production of ischemia in addition results in progressive hemorrhagic necrosis Complete devascularization of a large portion of the pancreas results in ischemic infarcts Occasionally a focal form of acute pancreatitis results from prolonged severe and extensive ischemia alone In some respects these observations are similar to those of Popper Necheles and Russell who have also combined ductal obstruction with vascular ligation but the latter investigators have stressed the importance of ductal occlusion and have considered the vascular effects additive

On the clinical side as Opie has pointed out the resemblance of the lesions of certain cases of acute pancreatitis to infarction of the pancreas led Brentano Korte Rossle Gerlei and Lowenthal to believe that acute pancreatitis could be caused by vascular thrombosis alone Opie also quotes Cecil as noting the frequent association of diabetes mellitus interacinar pancreatitis and arteriosclerosis However it appears from the description of the pancreatic lesions that in many instances the latter consisted only of interacinar fibrosis with some lymphocytic infiltration and it is doubtful if many of these represented acute pancreatic necrosis

Infarction of the pancreas has been observed by Hranilovich and Baggenstoss MacKenzie Gaster *et al* and others with occasional demonstrations of thrombosis or embolism of pancreatic arteries and these are considered a complication of arteriosclerosis Two such cases in patients 67 and 80 years of age are included in the present series of 22 cases attributed to vascular lesions

Recently Probstein Joshi and Blumenthal have shown that a complication of arteriosclerosis or syphilitic aortitis which involves pancreatic arteries in about one half of the cases in which it occurs is capable of producing acute pancreatitis This phenomenon atheromatous embolization is a process in which material from ulcerated plaques in the aorta is discharged into the blood stream and deposited as cholesterol crystals in arteries varying in size from 55u to 900u in diameter Since that report additional cases have been added and we now have 16 cases involving pancreatic arteries 13 of which show acute pancreatitis In general the development of the latter lesion appears to depend

upon the number of pancreatic arteries involved in the embolic process

A variety of other vascular lesions involving small arteries have also been reported in association with acute pancreatitis Richman cites Pollak as having observed such an association in disseminated lupus erythematosus with acute necrotizing vascular lesions in the pancreas and one of the 22 cases of acute pancreatitis attributed to vascular lesions in this study falls into this category Anderson has pointed out that periarteritis nodosa also may cause areas of localized pancreatic necrosis and three of our cases ranging in age from 46 to 67 years fall into this category Hranilovich and Baggenstoss have observed both parenchymal necrosis of the pancreas and infarction in association with malignant hypertension but arterial thrombosis could be demonstrated in only six of the seven cases showing infarction while no vascular lesions were found to account for the parenchymal necrosis and they were attributed to congestive cardiac failure and shock One of our 22 cases of pancreatitis attributed to vascular lesions was in a case of malignant hypertension but in the latter necrotizing arteriolar lesions similar to those usually encountered in the kidney were also found in the pancreas In a similar category with diffuse involvement of small vessels was one case of thrombotic thrombocytopenic purpura

Fat embolism associated with acute pancreatitis has already been mentioned The source of such emboli in fatty livers was first established by Weisel (1908) who found them in the pancreas of three cases all of which had pancreatitis Edmondson and Fields later reported a similar case and MacKenzie cites Davey as also having observed cases of this type In recent years Lynch *et al* and also Hartroft have again directed attention to this phenomenon The clogging of capillaries of the pancreas with lipid particles in cases of hyperlipemia with associated pancreatitis has already been noted in a previous chapter

c) ***Rupture of an Arteriosclerotic Vessel*** Rupture of an arteriosclerotic pancreatic artery with massive hemorrhage into the pancreas has been called pancreatic apoplexy and was recognized by some of the early workers as mentioned in the

introduction No cases of this phenomenon were encountered in the present series

d) *Vascular Spasm* There is also evidence that pancreatic *necrosis may be produced without permanent vascular occlusion* As Opie pointed out Blume (1897) exerted digital compression on pancreatic arteries for 10 minutes and small foci of necrosis resulted and Milisch Lewit and also Wulff have observed acute pancreatic necrosis resulting from local ischemia Nervous reflex mechanisms producing such vascular spasm have been stressed by Beneke and by Brutt and Marcus believed that such reflexes might account for acute pancreatitis when it occurs immediately following a large meal an operation trauma or poisoning in the absence of a lesion in the bile passage On the other hand reflex vasoconstriction as a reaction to edema or hemorrhage in the pancreas has been suggested by Zenker as a cause of shock in acute pancreatitis These reports however do not always carefully delineate spasm as a cause of pancreatitis from reflex vasoconstriction following initiation of the disease and which may be only a secondary contributing factor

In a series of reports Thal and coworkers have produced acute hemorrhagic pancreatitis either through the production of immunologic mechanisms or by the direct action of bacterial toxins which are able to permeate through pancreatic ducts In both instances the lesions are attributed to vascular changes Particularly noteworthy is the description of vascular changes by direct vision of gross lesions in anesthetized animals by transillumination coupled with subsequent histologic study The former show that the initial change following the development of pancreatic edema is a striking and rapid development of venous spasm and capillary stasis There is also an associated arterial spasm The engorgement of the capillaries and venules appear to make it highly probable that venous spasm precedes arterial spasm These coworkers have been able to show that areas of the pancreas exhibiting edema and induration are totally excluded from blood flow

Thus a compilation of the 22 cases of acute pancreatitis to which we have attributed a vascular basis appears as follows

Atheromatous embolization	13
Polyarteritis nodosa	3
Arteriosclerosis with pancreatic artery thrombosis	2
Collagen disease with necrotizing pancreatic arteritis	1
Malignant hypertension with necrotizing pancreatic arteritis	1
Thrombotic thrombocytopenic purpura with extensive involvement of pancreatic vessels	1
Transfusion reaction	1

As regards other arterial vascular changes in the pancreas in autopsy material as Smyth has pointed out the end stage evidence of the responsible factors may well have been destroyed without leaving a trace This is particularly pertinent regarding the vascular lesions described by Rich and Duff Such lesions most likely represent effects of pancreatic enzymes on vascular structures particularly in the light of recent work in our laboratories on the effects of pancreatic enzymes on vascular tissue components which have been discussed in later parts However such vascular alterations even as secondary phenomena may assume great importance since their occurrence may mean the difference between a localized relatively trivial form of the disease and a fulminating hemorrhagic process We have intentionally not separated pancreatic infarcts from acute pancreatic necrosis for reasons which will become apparent in Part III

Chapter 7

ALLERGIC FACTORS

The observation of acute pancreatitis in association with vascular lesions in disseminated lupus erythematosus and in polyarteritis nodosa has led to the consideration of acute pancreatitis as possibly having an allergic etiology Thus Thal and Brackney have been impressed with a similarity of the vascular lesions of acute pancreatitis to those observed in the dermal Schwartzman reaction They have introduced Meningococcus and E coli endotoxin into the pancreatic ducts of rabbits and goats and twenty four hours later injected dilute solutions of this toxin intravenously with resultant acute hemorrhagic pancreatitis They have advanced the theory that toxins in the bile and duodenal content may sensitize pancreatic vessels an acute hemorrhagic necrotic reaction is then produced in the sensitized tissues by the presence in the systemic circulation of a number of biologically unrelated substances

Subsequently Thal showed that in an experimentally produced Arthus reaction primary thrombosis of capillaries and venules results in classical hemorrhagic pancreatitis In a third report Thal and Molestina showed that the direct effects of a staphylococcus toxin on pancreatic vessels may also result in severe hemorrhage and necrosis of the pancreas The reports of Thal and coworkers have emphasized the role of blood vessels in the production of this disease and point out that allergic reactions constitute one mechanism by which such vascular lesions may be produced

Clinical support for an allergic etiology of pancreatitis is largely circumstantial For example Shaffer has described a case of acute pancreatitis with a serum amylase level of 300 in a 48 year old male coincident with the development of giant urticaria The response of the abdominal symptoms to pyribenzamine was

rather dramatic This patient had undergone an abdominal exploration for an attack of acute pancreatitis four years earlier

In the present series we have attributed one case to a possible allergic etiology This was in a 28-year old female with an acute diarrhea who had been placed on sulfathiazole therapy despite negative blood and stool cultures She developed renal shutdown and expired in uremia Autopsy revealed acute granulomatous lesions of the kidneys myocardium, liver and pancreas which were interpreted as an allergic response to the sulfathiazole While these granulomas as in any inflammatory reaction of this type contained a vascular component this was not considered the most important part of the lesion The reaction in the pancreas was more in the nature of an inflammatory reaction then a hemorrhagic necrotic lesion as observed by Thal *et al* in experimental animals

Chapter 8

THE IDIOPATHIC GROUP

As shown in Table III we have placed over one third of the cases of acute pancreatitis in this category. This has been done on the basis that either no disease was present which might even remotely be connected causally with acute pancreatitis or that there were only diseases with a suggestive etiologic relation. The preceding presentation has dealt with such diseases in the latter category as chronic cholecystitis, diabetes, various hepatic diseases, uremia, gastric or duodenal ulcer. In order to test the validity of the statistical correlations which have been made with respect to such diseases, a similar comparison has been made with a disease which would be expected to be unrelated causally to acute pancreatitis, namely, cancer (Table XIII). It is obvious from these data that the frequency of cancer in the total autopsy population and in the cases of acute pancreatitis is about the same.

TABLE XIII

MALIGNANT DISEASE AND ACUTE PANCREATITIS

Age Group	Without Pancreatitis: Male	Per Cent	Female	Per Cent	With Pancreatitis: Male	Per Cent		Female	Per Cent	
0-10 yrs	7	1.4	5	1.1				1	6.3	(16.7)
11-20 yrs	6	1.2	5	1.1						
21-30 yrs	11	2.2	7	1.5						
31-40 yrs	36	7.1	40	8.6						
41-50 yrs	47	9.3	78	17.1	6	31.6	(11.3)	7	43.8	(8.2)
51-60 yrs	134	26.6	146	31.9	3	15.8	(21.9)	2	12.5	(1.4)
61-70 yrs	160	31.7	101	22.1	6	31.6	(3.6)	1	6.3	(1.0)
71-80 yrs	85	16.9	50	10.9	3	15.8	(3.4)	5	31.3	(9.1)
81 +	18	3.6	25	5.5	1	5.3	(5.3)			
Total	504	2[illegible]3	4[illegible]7	30.1	1[illegible]	20.[illegible]	(3.6)	16	23.2	(3.4)

Per cent of autopsy population without pancreatitis in corresponding sex group.
Per cent of autopsy population with pancreatitis in corresponding sex group.
Figures in parenthesis represent per cent of all cases of malignant disease in corresponding sex and decade and in bottom horizontal column per cent of total cases of corresponding sex with cancer.

The following tabulation compares the frequency of these diseases in the idiopathic group with the incidence in the total group with pancreatitis Hepatic diseases have been omitted since all cases have been included in the various groups with definitive etiology *It is evident from this tabulation that only diabetes* was slightly more frequent in the idiopathic group than in the total group of pancreatitis cases

Disease	*Idiopathic Group*	*Total Group with Pancreatitis*
Chronic Cholecystitis		
with Lithiasis	26 3 per cent	30 0 per cent
Gastric or Duodenal Ulcer	3 5 per cent	17 1 per cent
Diabetes	17 5 per cent	13 5 per cent
Uremia	14 0 per cent	21 5 per cent

It seems safe to conclude therefore that these diseases probably contribute no more etiologically to the development of pancreatitis in this group than in the groups with a definitive etiology

Perhaps the most striking feature of the idiopathic group was the frequency of associated thrombotic or embolic disease Thirty six cases (63 1 per cent) of these types were found 17 showed embolic phenomena with infarction of the kidney spleen liver lung intestine or lower extremity and in some of these there were also instances of coronary or cerebral thrombosis which were not included in the following two groups Coronary thrombosis without embolic phenomena was present in 16 additional cases and cerebral occlusion in three In three other cases not included in the 63 1 per cent acute pancreatitis was a terminal development incident to severe shock in markedly arteriosclerotic patients Thus over two thirds of the cases in the idiopathic group have findings which suggest a vascular etiology

It is evident then that in this as in most series of cases of acute pancreatitis if one takes into account all instances with a definitive etiology and even adds those with some suggestive etiology, there remains a sizeable group of cases probably about 10 per cent in which neither the history nor the autopsy findings reveal significant causal factors

Chapter 9

COMPLICATIONS AND SEQUELAE

a) *Mortality* Since we are dealing here with an autopsy group comparison may be made with clinical series on the basis of those of the present cases of acute pancreatitis which were of such severity as to constitute the primary cause of death Accordingly the 163 cases of acute pancreatitis were evaluated as to whether the pancreatic lesion constituted the principal cause of death, a contributing cause or only an incidental finding as shown in the following tabulation

	Number of Cases	*Per Cent*
Principal Cause of Death	17	10 4
Contributing Cause of Death	69	42 3
Incidental finding	77	47 2

Of the 17 cases which were considered the principal cause of death two were in the metabolic group and both were males ages 42 and 46 one was a case of biliary obstruction in a 46 year old female and one was in the infectious group a 78 year old male three were on a traumatic basis and of these two were males ages 59 and 61 and the third a female 61 years of age there were also three cases on a vascular basis a male aged 69 and two females 52 and 76 years old seven were in the idiopathic group four males ranging in age between 36 and 51 years and three females between 61 and 65 years of age Thus six of the 17 cases almost one third were less than 50 years old the relative youthfulness of this group would tend to minimize the importance of such a causal factor as vascular disease and emphasize biliary obstructive metabolic allergic traumatic and infectious factors It is also pertinent from an etiologic standpoint that in the series of Healey *et al* in 60 per cent of the cases of acute pancreatitis under age 50 the pancreatic disease was considered the primary cause of death as compared with 40 6 per cent of the cases over age 50 In our series in 15 0 per cent of the cases under age 50 the pancreatic disease was considered the

primary cause of death as compared with 9 6 per cent over age 50

If one accepts the group in which pancreatitis was considered to be the primary cause of death as analogous to mortality data in a clinical series then the incidence figure of 10 4 per cent is comparable to the rate of 12 per cent reported by Baker and Bartlett the 14 per cent found by Siler and Wulsin and the 11 5 per cent reported by MacKenzie In fact the close agreement of these figures is rather impressive

b) *Extra-abdominal Fat Necrosis* Widely disseminated fat necrosis in acute pancreatitis was first reported by Balser (1880) who described such foci in the mediastinal and pericardial fat Subcutaneous areas of fat necrosis were first described by Hansemann Chiari and Blauvelt and in the medulla of the long bones by Ponfick More recently Vogel has reported a case of acute hemorrhagic pancreatitis in which disseminated fat necrosis was found in the heart adrenals and ovary in addition numerous areas of focal cerebral demyelinization were found Cerebral lesions associated with acute pancreatitis have also been observed by Rothermic and von Hamm Perry has reported a case with extensive fat necrosis throughout the thoracic cavity and cases involving the medulla of bones most often the ribs have been reported by Scarpelli In general it appears that such disseminated foci occur in cases with widespread abdominal fat necrosis and not in the acute hemorrhagic form of pancreatitis

Hasche Klunder has observed a case of acute pancreatitis in a Meckel s diverticulum coincident with the same disease in the pancreas proper and Longmire and Wallner have reported two cases of a similar nature one also involving a Meckel s diverticulum and the second ectopic pancreatic tissue in the jejunum This may represent an unusual form of dissemination although neither of these two reports consider such a mechanism Bradley and coworkers have observed hemorrhagic pancreatitis in gastric heterotopic pancreas but this may have been the result of direct extension from the pancreas proper

While such disseminated foci involving extra abdominal organs are generally considered to be a rare occurrence Roberts

et al have found pericardial and mediastinal involvement in 12 per cent of 25 necropsied cases and Scarpelli has found bone marrow involvement in 10 4 per cent of 67 autopsies with acute pancreatitis

In reviewing the literature on this subject Rostock has pointed out three principal hypotheses as to mechanism i e (1) Direct contact (2) Blood stream transport and (3) Lymphatic transport He concluded that most of the evidence supported the third Perry later showed that the intraperitoneal injection of lipolytic substances or damage to the pancreas and its ductal system in rats resulted in fat necrosis not only in the peritoneal cavity but also in the subpleural pericardial and mediastinal fat By combining graphite with pancreatin in the injection medium he was able to demonstrate a continuity between the peritoneal and thoracic lymphatic channels as well as a close and constant association between these delineated channels and the sites of fat necrosis While lymphatic spread of lipase might also account for the lesions in bone marrow and in sites of ectopic pancreatic tissue they would not account for the cerebral lesions Lynch has suggested that fat emboli emanating from fatty livers may produce both the cerebral lesions and the acute pancreatitis and in one case in the report of Longmire and Wallner such a fatty liver due to chronic alcoholism was present On the other hand Vogel has produced cerebral lesions similar to those seen in human cases of acute pancreatitis by the intracerebral or intracarotid injection of pancreatic lipase and suggests blood stream transport as a causal mechanism

No extra abdominal foci of fat necrosis were reported in any of the 163 cases in the present series However since there were many prosectors involved in the accumulation of this material it is possible that such cases have been overlooked Because of the cerebral involvement noted above an attempt was made to compare the frequency of focal encephalomalacia in cases of pancreatitis with the incidence in the total autopsy population A frequency of 11 0 per cent was found in the former and 9 4 per cent in the latter and this was not considered a significant difference

c) *Fat Embolism* Fat embolism as a cause of pancreatitis has already been considered but foci of fat necrosis in the pancreas may also gain entrance into the circulation and embolize Such emboli have been demonstrated by Lynch in the kidney but in addition he has suggested that the cerebral and vascular lesions described by Vogel *and others may also have been due* to fat emboli According to Lynch many cases probably die from embolization *of the heart lungs or brain and he attributes the* cyanosis in pancreatitis to fat embolization of the pulmonary capillary *bed Other cases may die of nephrosis from renal em*bolization If the patient survives long enough following em*bolization of this type the high serum lipase concentration may* result in splitting of embolized fat so that the latter no longer *takes the neutral fat stains* and for this reason such *emboli as* well as foci of extra abdominal fat necrosis may be overlooked

d) *Visceral Complications* Fisher and McCloy have observed focal necrosis of the liver associated with bile stasis in some cases of pancreatitis and more widespread changes with hemorrhage and cellular degeneration in others all of these appear to be secondary to biliary tract obstruction and not directly a complication of acute pancreatitis Pericholangitis and fatty metamorphosis of the liver have also been observed and these may be causally related in varying degrees rather than complications The only genuine complication of the liver appears to be the fat necrosis resulting from the reflux of pancreatic lipase into the hepatic ducts as reported by Schiller

Necrosis and perforation of the common bile duct with bile peritonitis has been observed by Zaslow apparently by involve*ment of the intrapancreatic and intraduodenal portions* of the common duct in the necrotic process

Berk has mentioned a poorly defined impairment of renal function associated with acute pancreatitis and Gaberman and coworkers a renal anoxic syndrome Several investigators (Renner Wilkey *et al* and others) have noted a lower nephron syndrome which terminated *fatally in patients in whom acute pan*creatitis developed after prostatectomy This has been attributed to the increased *circulating trypsin since the work of Mirsky and*

Freis indicates that proteolytic enzymes from injured tissues may damage the kidneys Dehydration and shock incident to the pancreatitis are other factors to be considered in this regard Lynch has described four cases in which acute pancreatitis was associated with nephrotic renal damage in two of which widespread fat embolism was demonstrated Trout and Albertson have stressed the frequency of albuminuria in acute pancreatitis and glycosuria has also been observed

We have encountered no instances of hepatic or biliary tract disease which might be considered a complication of acute pancreatitis There were two cases of abscesses of the liver in patients in the infectious group with septicemia in which the latter were considered metastatic as were also areas of abscess formation in the pancreas Centrohepatic degeneration sometimes with frank necrosis was found in several cases of fulminating pancreatitis, but this was attributed to the state of shock incident to the pancreatic disease rather than a direct complication of the pancreatitis

As to renal complications two cases showed a perinephric abscess involving also the upper pole of the left kidney which was considered to be due to an extension of an abscess of the tail of the pancreas associated with acute pancreatitis There were four cases with acute pancreatitis following prostatectomy three of these showed acute suppurative disease of the kidneys resulting from prolonged prostatic obstruction and the fourth developed a lower nephron syndrome following postoperative bleeding and shock Thus there were no instances of renal disease which might be attributed directly to the acute pancreatitis

e) *Abscess and Pseudocyst Formation* According to Bockus abscesses develop in those cases of acute pancreatitis which are on a suppurative basis and the abscess content is also evidently suppurative rather than necrotic from the beginning either as a result of lymph borne or hematogenous infection or from extension of inflammation from an adjacent organ Our experience has been somewhat different while most of the cases with abscess formation were indeed in the infectious group as the following tabulation shows there were also a number of abscesses in other groups

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In recent years there have been a number of reports on this subject (McWhorter, Judd *et al*, Sinclair, Kune, Probstein and others), but these have dealt primarily with the technique of surgical therapy. Gambill and coworkers have reported a frequency of pseudocyst in about 10-15 per cent of cases with recurrent pancreatic disease, but it is not clear how many of these may have been comparable to the cases we have considered as sterile abscesses. There was only one pseudocyst in the present group (0 6 per cent), but in the clinical series reported from this hospital by Probstein the incidence was 1 4 per cent. In the same series the frequency of abscesses was only 1 9 per cent as compared with 10 4 per cent in the present autopsy group. Thus pseudocysts were diagnosed more frequently in clinical cases, while abscesses were found more frequently at autopsy.

One distinction has been made between pseudocysts and abscesses. The former are characteristically located outside the parenchyma of the pancreas and as a rule occupy the lesser omental sac, thus having no wall of their own and no special lining; they are bounded by the peritoneum of the omental sac and the adjacent organs. Nevertheless, necrotic debris from the pancreas during an acute attack may be released into the peritoneal cavity, where its enzyme content may destroy other tissues and form an abscess. Thus several of the cases classed as abscesses, including the two already noted which extended to the perinephric region, were extra-pancreatic.

f) *Miscellaneous Complications*. Usui has reported muscle hematomata in cases of acute hemorrhagic pancreatitis, but we have not found this complication in the present series. Pleural effusion has been noted by Lipp and Aaron and by Weiner as a result of pancreatitis, but in the present series pleural effusion was found in 19 0 per cent of cases with acute pancreatitis and in 37 2 per cent of the total autopsy population.

Hardy and Bowlin have stressed the high frequency of ascites associated with pancreatitis. This has been true in the present series only in those instances in which the pancreatic disease was considered the primary cause of death. These workers also call attention to obstruction of the small intestine in some in-

Abscess Formation in Acute Pancreatitis

Etiologic Group	*Single Attack of pancreatitis*	*Recurrent Attacks*	*Total*
Infectious	9	1	10
Obstructive	1	1	2
Metabolic	1	0	1
Traumatic	0	0	0
Vascular	0	0	0
Allergic	0	0	0
Idiopathic	3	1	4
Grand Total	14	3	17

Data on the frequency of the complication of abscess formation are rare In many instances it is mentioned only in connection with recurrent pancreatitis Siler and Wulsin report an incidence of 11 0 per cent of 164 cases of acute pancreatitis and the frequency in the present group is 10 4 per cent The incidence in the 141 cases with less than three attacks of acute pancreatitis was 9 9 per cent and in the 22 cases with recurrent disease 13 6 per cent It is pertinent that in the present series cavities containing semi solid or semi liquid content were classed as abscesses regardless of the presence or absence of suppuration while the single case with a liquid content was considered a pseudocyst Perhaps other investigators would have considered all of the non suppurative cases as pseudocysts

Opie believed that socalled pseudocysts form as the result of degenerative changes affecting the interstitial tissue of the pancreas and that their formation and increase in size is dependent in large part upon the presence of the irritant and corrosive action of the pancreatic secretion He also recognized that cysts containing blood can arise as the result of hemorrhage into the pancreas and these have been termed apoplectic cysts In most instances pseudocysts are believed to arise as a result of trauma and Lazarus has produced small cysts in dogs with crushing injuries to the pancreas In 33 of 117 cases of pseudocyst formation Korte found that abdominal injury preceded the appearance of a palpable mass and Lazarus reported eight additional cases of similar nature Such traumatic cysts usually contain blood as well as enzymes similar to those found in the pancreatic juice

be related to the diabetes and the hematemesis and melena either to gastritis or the formation of esophageal varices While many of these cases are associated with cirrhosis of the liver Snider and Nelson have recently reported a case of bleeding esophageal varices resulting from portal hypertension incident to portal vein obstruction the latter was due to an enlarged pancreas from recurrent attacks of pancreatic disease The liver was grossly normal despite a history of alcoholism and portal obstruction was apparently not due to hepatic disease Gambill has observed the unusual event of a fatal gastrointestinal hemorrhage when a spicule of calcium in the head of the pancreas eroded through the duodenum and into an artery While in many instances with recurrent attacks elevated serum lipase and amylase levels may occur they are also often within normal limits or even low

Unlike cases with an initial attack of acute pancreatitis these forms of pancreatic disease are more common in males with a ratio of between 3 and 6 to 1 An age distribution ranging between 10 and 75 years has been observed but it is most common in the fourth and fifth decades All of the etiologic considerations which have been presented with regard to acute pancreatitis have also been applied to this disease but particular emphasis has been placed on the frequency of a history of alcoholism It is pertinent however that Gross and Comfort have pointed out that associated biliary tract disease may be a result rather than a cause of the pancreatitis and Sachs and Partington have recently demonstrated distortion of the common duct with resultant obstruction when inflammatory disease produces an enlargement of the head of the pancreas In general cases of pancreatitis are not placed in this category unless these is evidence of more than three severe bouts of acute disease In the series of Gambill *et al* a history of repeated episodes have ranged from three months to 34 years with an average of 7 5 years and in the group studied by Baker and Bartlett from 12 to 60 months The frequency of attacks have varied from once every four years to once daily or weekly

Edmondson and coworkers have collected 62 instances of this disease based on autopsy findings and this represented an inci

stances the swollen pancreas may compress the second portion of the duodenum sufficiently to produce obstruction However, most instances are due to paralytic ileus as has been pointed out in Part IV

The complication of pancreatic fistula formation is also mentioned by Hardy and Bowlin Usually these occur on a traumatic basis and in this series there are two cases with a pancreaticoduodenal fistula following gastric surgery

g) ***Recurrent Acute Pancreatitis*** As Edmondson *et al* have pointed out the effects of repeated attacks of pancreatitis was a popular subject for authors during the latter 19th and early 20th Centuries Thus among the early workers to observe and describe such disease were Claessen (1842) Friedreich (1878) Oser (1898) Opie (1902 1910) Mayo Robson and Cammidge (1907) and Gruber (1929) In more recent years a revival has taken place with studies by Stern Svarts Maimon *et al* Comfort and coworkers Gambill and associates Baggenstoss Doubilet and Mulholland Wilbur Martin and Canseco MacKenzie Ray and Console Klatskin and Gordon and others

Various apparently unrelated forms of acute and chronic pancreatitis have been described over a period of many years but a clearcut concept as to any inter relationship remains to be elucidated At the present time such varied terminology as Chronic Pancreatitis Chronic Relapsing Pancreatitis Acute Recurrent Pancreatitis and Chronic Pancreatitis with Lithiasis" are encountered in the literature In general older workers placed this group in three categories (1) Those characterized by recurrent acute attacks (2) Those with findings of pancreatic deficiency and (3) Those with pancreatic lithiasis with or without pain but with evidence of pancreatic insufficiency

In most instances these diagnostic terms are used to describe a disorder of the pancreas characterized by recurrent attacks of upper abdominal pain with disturbances of function of both the acinar and islet cells The sequelae of such disease processes have been listed as diabetes steatorrhea creatorrhea pseudocyst or abscess formation and calcification frequently demonstrable by x ray Other complications are malnutrition hematemesis and melena pylephlebitis and peripheral neuritis The latter may

current attacks. While the extent of such calcification does not necessarily parallel the severity of the disease, the complications of steatorrhea and diabetes are more common in those cases with multiple calculi. Diabetes is present in 15 to 25 per cent and is generally mild, while steatorrhea occurs in 25 to 30 per cent of cases. On the other hand, Gambill also recognizes that there are cases in which, despite repeated attacks over a period as long as 10 years, pancreatic calcification, diabetes and steatorrhea do not occur. Loeffler and also Elman have recognized that there are many cases with multiple mild attacks of "transient acute pancreatitis" in which no recognizable residua develop in the pancreas.

There are also certain special forms of recurrent pancreatitis which are recognized. Gross and Comfort as well as Klatskin and Gordon have stressed the occurrence of hyperlipemia with xanthomatosis and lipemia retinalis in certain patients. Some of these belong in the group of the essential familial type. It is not known whether the hyperlipemia is causal in nature, a result of the disease, or merely coincidental. Comfort and Steinberg have pointed out that there is, in addition, a hereditary (familial) form of recurrent pancreatitis, and Comfort and coworkers have now collected at least six such cases. The disease appears to be transmitted as a Mendelian dominant and is also associated with hyperlipemia. It appears to begin in childhood and shows a predominance in females. Neither alcoholism nor gallstones play a role in this group of cases, and hyperlipemia appears not to be a causal factor. It is felt that this form of pancreatitis is due to an inherited metabolic defect.

Evidence for another form of recurring hereditary pancreatitis has recently been reviewed by Gross *et al.* This resembles the nonhereditary disease, including such complicating features as diabetes, pancreatic calcification and insufficiency, pseudocyst formation, steatorrhea and azotorrhea. It almost always begins in childhood and affects females about 1.5 times as frequently as males. It appears to be transmitted by a nonsex-linked Mendelian dominant gene. The distinctive feature is an excessive urinary excretion of lysine, and the evidence suggests some hereditary defect in intermediate protein metabolism.

dence in the total autopsy population of 0 18 per cent In none of these was there a definitive picture pointing to pancreatic inflammatory disease They attributed this to (1) inadequate history (2) lack of pain as a prominent symptom and (3) a low index of suspicion on the part of the examining physician In obtaining retrospective clinical information it was found that in 38 7 per cent there was evidence of excessive use of alcohol 19 of these showed fatty cirrhosis of the liver and there were three cases of portal cirrhosis without alcoholism Diabetes was present in 29 per cent, but only two of these were also alcoholics In only four cases was the pancreas a probable source of pain Jaundice was present in three cases and biliary calculi in the ampulla of Vater in two None of the 62 cases gave evidence of steatorrhea Despite the symptomless course 16 had acute pancreatitis at necropsy and in four it was the cause of death Calcium in ductal debris was found in only one case the remaining 61 showing no evidence of lithiasis

On the other hand Comfort and coworkers have stated that chronic pancreatitis is often complicated by the presence of calculi Edmondson *et al* in another report found 26 patients in 3000 autopsies with such calculi an incidence of 0 33 per cent Again a history of alcoholism was present in 15 of these cases 14 of whom had multiple stones and the 15th a single calculus Diabetes was seen more often in non alcoholic patients there were five cases of diabetes in the 11 non alcoholics and three among the 15 alcoholics These authors state that from an etiologic standpoint it is difficult to relate either clinically or pathologically all of the pancreatic stones to previous attacks of pancreatitis and there was little or no chronic inflammatory re action Opie and Friedreich have also commented upon the fact that pancreatic lithiasis is frequently symptomless King and Waghelstein point out that calcification in the parenchyma which is sometimes referred to as false stones may occur in areas of necrosis of parenchyma or of fat necrosis Diffuse cal cification of this type is rare and there is evidence that it may undergo resorption

Gambill and Pugh have reported that calculi in pancreatic ducts are found in about one third to one half of cases with re

adults similar to fibrocystic disease in infants are seen in uremia hepatic disease high intestinal obstruction, and in chronic ulcerative colitis including a thick viscid pancreatic secretion but without the development of ductal lithiasis

On the other hand Davis has pointed out that the pancreas may be almost completely absent in infants and yet unaccompanied by a celiac syndrome and Bostick and Rinehart have remarked that adults may not reveal a celiac syndrome until 90 per cent or more of the acinar tissue has been destroyed These observations suggest that the succus entericus may contain sufficient proteolytic and lipolytic enzymatic activity to compensate to some extent for the pancreatic loss In fact Hansman has remarked that the excess of intestinal lipase is so great that it must seldom happen that even in the absence of pancreatic secretions the fats are not hydrolyzed unless for mechanical reasons Such observations would tend to support the concept of multiglandular involvement including the intestinal glands as proposed by Farber perhaps even in some adult cases

A history of more than three attacks of acute pancreatitis was obtained in 22 of the 163 cases in this series (13 5 per cent) The longest case covered a period of 27 years during which there were nine hospital admissions for major episodes and there were also numerous minor episodes which did not require hospitalization There was not a single patient with ductal lithiasis in this group On the other hand in the total autopsy population there were three cases with multiple ductal lithiasis without a history of alcoholism cirrhosis of the liver or diabetes and also without clinical or historical evidence of acute pancreatitis

It would appear from the foregoing that certain patients have mild recurring attacks of acute transient pancreatitis which leave no stigmata of chronic pancreatic disease while in others the attacks are of sufficient severity so that with progressive scar formation a state of pancreatic insufficiency eventually results On the other hand there are also certain diseases which produce associated changes in the pancreas similar to those seen following severe acute episodes but in which there is no evidence that acute pancreatic inflammatory disease has ever occurred Similarly there are instances of pancreatic ductal lithiasis without

Still a third special form is fibrocystic disease of the pancreas in infants and children It appears that by about 1913 Garrod and Hurtley had associated this lesion of the pancreas with congenital diarrhea in children and in 1935 Parmelee proposed that this pancreatic lesion be recognized as a subtype of celiac syndrome Harper Rauch *et al* and Anderson subsequently presented criteria establishing this as a clinical entity Since about 1940 a vast literature has accumulated on the subject which has been adequately reviewed by Baggenstoss and coworkers Wiglesworth Farber and others Considerations of etiology include (1) infection (2) vitamin A deficiency (3) congenital atresia of the pancreatic ducts (4) abnormal pancreatic secretion and (5) congenital deficiency of secretin Infection is probably a secondary phenomenon as is vitamin A deficiency which is probably due to a failure to absorb the fat soluble vitamins Support for the contention that the disease is due to a congenital atresia of the pancreatic ducts comes from a variety of anatomic studies which have been reviewed by Baggenstoss and coworkers Farber has presented evidence that the condition is systemic the primary fault being an alteration of the character of the secretions within many glandular structures and from this has been derived the descriptive term mucoviscidosis by which many pediatricians identify the disease Farber has suggested that this is due to excessive vagus action with the production of a viscid glandular secretion or a defect in mucin liquefaction A congenital absence of secretin or some defect in the mechanism of its release has also been suggested included in the latter is the possibility that secretin is destroyed as suggested by the discovery of a secretinase in dogs by Greengard *et al*

As has been pointed out in a subsequent part the pathologic changes in fibrocystic disease have much in common with recurrent acute pancreatitis in adults but superimposed bouts of acute inflammation have not been stressed Most known cases have been found in infancy and early childhood and are characterized by steatorrhea bronchitis and subsequent nutritional deficiency and bronchopneumonia but Ivy and Gibbs suggest that the disease may also occur in older individuals with steatorrhea bronchitis and nutritional liver disease Changes in the pancreas of

the bacteria or an indirect effect associated with intestinal or biliary pancreatic stasis Since similar infectious processes as in the case of peritonitis are so often not associated with acute pancreatitis conditions which create a state of susceptibility of the pancreas loom particularly important

The same may be stated regarding bile reflux mechanisms whether they occur on the basis of organic obstruction as demonstrated by Opie or secondary to edema or spasm of the ampulla of Vater or the duct of Wirsung as proposed by Archibald Doubilet and Mulholland and others Such reflux when acting alone is apparently capable of producing only a mild or moderate pancreatitis The demonstration by cholangiography of the frequent reflux of bile into the pancreas without the clinical manifestation of acute pancreatitis also indicates the requirement of some pre existing state of susceptibility Similarly obstruction of the pancreatic duct alone as proposed by Rich and Duff results in only a mild pancreatitis as shown by the experiments of Lium and Maddock Wangensteen and coworkers by Coffey Hess as well as by Popper *et al*

In the case of metabolic factors dietary deficiency may represent a means of conferring such a state of susceptibility on the pancreas for the inflammatory and necrosing components are of minor intensity in such instances Hepatic disease may have *its effect either by producing a protein deficiency through im*paired synthesis by producing a hyperlipemia or by supplying a source of fat embolism to the pancreas Toxic agents such as alcohol may act by producing a duodenitis with resulting spasm of the ampulla of Vater hepatic dysfunction and/or a direct *toxic effect on pancreatic tissue* and *other toxic* agents may also act in one or more of these ways

Traumatic agents appear to have their effect by causing the release of enzymes from injured acini and ducts and blood from traumatized vessels into the interstitial tissues but even here in many instances as Dunphy *et al* have stressed injury to vascular structures with thrombosis cannot be excluded as having an important role

evidence of antecedent acute pancreatic disease It is therefore small wonder that confusing diagnostic terminology exists

The relation of ductal lithiasis to inflammatory disease of the pancreas also remains in doubt There is no evidence that calcification of either necrotic parenchyma or fat necrosis in any way contributes to the formation of intraductal stones Nor is the evidence convincing that inspissated viscid secretion in dilated ducts undergoes secondary calcification Yet the development of lithiasis is generally considered as due to antecedent acute pancreatitis and consideration appears not to have been given to the possibly that calculus formation may in the first instance be unrelated to acute pancreatitis The observations of Cope *et al* of acute pancreatitis associated with hyperparathyroidism suggests one mechanism by which such calculi may form Dawson and Struther Smith and Cooke Rogers *et al* Martin and Canseco and Page have all reported cases of hyperparathyroidism and calcification of the pancreas Certain of the seven cases included in these reports showed widespread parenchymal deposits but in at least three of the seven there were ductal stones Edmondson *et al* have also remarked concerning the association of pancreatic lithiasis and pulmonary tuberculosis It is therefore conceivable that pancreatic lithiasis may occur as part of a disease entity unrelated directly to pancreatitis but that the presence of such ductal occlusion may render the pancreas susceptible so that subsequent insult even of minor degree would produce acute inflammatory disease Needless to say if such insult does not occur pancreatitis may not develop as in the three instances in our autopsy population

SUMMARY

In evaluating the relative importance of each of the etiologic categories one is impressed with the frequency with which both on an experimental as well as a clinical level there appears to be an interplay of several causal factors As has been pointed out in pancreatitis which appears to be on an infectious basis it is not always certain whether the process represents a direct effect of the infectious agent the activation of saprophytic organisms resident in the gland an effect of a toxin liberated by

attacks remain largely a mystery When calculi are present they may perhaps confer a state of susceptibility but other susceptibility factors must also exist since in most instances recurrent episodes are not associated with ductal lithiasis

One aspect of mortality deserves emphasis While our data are not as striking as those of Healy *et al* it nevertheless appears that when pancreatitis occurs before age 50 it is more often likely to be the primary cause of death than when it occurs after age 50 In this connection the role of pancreatic elastase may be particularly important as discussed in Parts II and III

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The role of vascular lesions is particularly difficult to evaluate Severe arteriosclerotic lesions may be present without pancreatitis although such vascular alterations may be important in conferring a state of susceptibility on the pancreas as indicated by the high incidence of pancreatitis in uremic patients On the other hand sudden occlusions whether from embolic phenomena as pointed out by MacKenzie or fat or atheromatous emboli may result in acute pancreatitis even in the absence of severe arteriosclerosis of the pancreas On an experimental level the injection of oily substances has a similar effect Two considerations remain to be evaluated in this regard (1) the state of susceptibility of the pancreas in which ductal obstruction may play a role and (2) the state of the collateral circulation Anatomic studies by Olsen and Woodbourne show a rich collateral supply Impairment of the latter may make a single or only several occlusions effective otherwise multiple emboli may be required as we have pointed out with regard to atheromatous emboli

In allergic phenomena the mechanism of injury may be related to an antigen antibody reaction with a release of histamine and a direct effect of the latter on pancreatic tissue or the production of an allergic vasculitis with impairment of the circulation to the pancreas

Thus through all of these considerations there remains unresolved whether any single causal mechanism in a given situation has its effect directly on pancreatic tissue or merely confers a state of susceptibility on the pancreas so that the latter may then be injured by other factors This problem has been dealt with again in Part II

The complications and sequelae which has been dealt with are those with anatomic manifestations but there are a number which are largely biochemical and they have been discussed in Part II The type of etiology may determine in part at least the kind of complication Thus abscess formation is most common in suppurative pancreatitis while pseudocyst occurs most often as a complication of fulminating hemorrhagic or traumatic pancreatic disease Similarly the development of a pancreatic fistula usually occurs on a traumatic basis The reasons for repeated

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PART II

PATHOLOGIC PHYSIOLOGY

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PATHOLOGIC PHYSIOLOGY

As a source of powerful digestive enzymes the pancreas is a seat of peculiar biochemical and physiologic processes In organs such as the pancreas where potentially self injurious agents are produced (the stomach with acid and pepsin is another example) there exists a conflict between attack and defense and sometimes the intensity of the former or the poverty of the latter will be the paramount factor in the pathogenesis of pancreatitis To a great extent Part I has dealt with agents and circumstances which cause a shift of this balance in one direction or the other Because of such considerations an understanding of the factors present in this balanced state are important and they are first presented here They relate only to the exocrine portion of the pancreas since there is no evidence indicating that substances capable of injuring pancreatic tissue are produced by the islets nor is there any evidence that islet activity in any way inhibits the activity of the injurious agents under consideration Subsequent sections of this part deal with intrapancreatic effects of the self injurious substances produced in the pancreas and with effects on body fluids and other organs

gastric pepsin and acts on both native proteins as well as peptones and proteoses causing their breakdown to polypeptides and peptides Shepovalnikov showed that the acinar cells secrete an inactive trypsinogen which is then carried into the duodenum where it is activated by enterokinase a duodenal secretion to active trypsin However other substances may also activate trypsinogen since even contact with normal skin results in a digestive action other activators are present in tissue juices pus and probably also calcium ion in concentrations above 0 02 molar can activate trypsin despite the fact that some ionizable calcium is normally present in pure pancreatic fistula secretion

Another pancreatic enzyme chymotrypsin closely resembles trypsin in its action It also exists in the pancreas in an inactive form chymotrypsinogen which is activated only in the presence of active trypsin There are still other proteolytic enzymes which split intermediate products of protein digestion into simple end products Cowgill has listed additional proteolytic substances occurring in the pancreatic secretion or in the pancreas itself i e carboxypeptidase aminopeptidase erepsin ribonuclease guanase adenase collagenase and there are undoubtedly others

An additional pancreatic proteolytic enzyme elastase deserves particular emphasis because of its possible role in the pathogenesis of acute hemorrhagic pancreatitis Balo and Banga have extracted this enzyme which is capable of producing the lysis of elastic tissue In assaying human pancreases they found that the elastase content is reduced in elderly subjects They have also reported that in addition to its action on elastin it can solubilize collagen when the latter has first been altered from its native state as by heating According to these investigators one component common to both these structural elements is a mucoprotein and it may be on this component that the enzyme acts In this connection it is pertinent that Peplar and Brandt believe this enzyme to be a chondrosulfatase identical with an enzyme obtained from Ps pyocyanea and P vulgaris On the other hand Hall has reported the complete separation of two enzymes from crude elastase preparations which he has designated as E_1 and F The first has no proteolytic effect and appears to activate E Hall believes that E_1 reacts with the mucoid fraction of the elas

Chapter 10

NORMAL PHYSIOLOGY OF THE PANCREAS

a) ***Pancreatic Enzymes and Their Secretion*** Knowledge of the biochemical characteristics of substances elaborated by the pancreas stem from the observations of Claude Bernard (1850) who cannulated the pancreatic duct in dogs and collected three basic ferments i e protein splitting starch splitting and fat splitting substances Subsequently Heidenhain (1875) described the histologic mechanisms of cellular secretion and by the end of the 19th Century Pavlov had demonstrated the importance of the vagus nerve in controlling and stimulating pancreatic secretion and the role of pancreatic juice in intestinal digestion Then Bayliss and Starling (1902) described the formation of secretin and its mechanism for stimulating pancreatic secretion The demonstration that secretin is formed in the duodenum and carried by the blood to the pancreas where it excites secretion of pancreatic enzymes provided the first evidence that the intestinal tract is a source of endocrine substances

Normal pancreatic secretion is clear colorless and slightly mucoid it is 98 per cent water and the rest consists of protein and organic matter The juice is always alkaline with a pH varying from 7 10 to 8 65 and the pH is largely dependent upon the relative proportions of chloride and bicarbonate Miller and Wiper have estimated that about 6 gm of protein per day is lost in the pancreatic secretion hence the relatively large protein requirement of this gland for proper function It has been estimated that the total volume of pancreatic secretion in twenty four hours is about 700 cc

Trypsin is the chief proteolytic enzyme in this secretion and was first described by Kuhne (1867) and first isolated in chemically pure form by Northrop and Kunitz (1932) The latter investigators subsequently prepared in pure crystalline form chymotrypsin and the inactive forms chymotrypsinogen and trypsinogen Trypsin is a more powerful proteolytic ferment than

other than elastase Lipo and mucoprotein complexes with elastin may be formed at points where the polar amino acids are positioned hence the action of elastase would result in the release of the lipid or polysaccharide portions of these complexes but Yu has found no evidence that elastase has either a specific lipolytic or mucolytic activity

The pancreas also contains two amylolytic enzymes amylase or diastase and maltase Amylase normally occurs also in the saliva leucocytes plasma and urine It hydrolyzes starches at an optimum pH of 7 producing maltose and a disaccharide The amylase normally present in the blood is derived in part from sources other than the pancreas since even after total pancreatectomy the enzyme is still present in blood samples Maltase present in smaller quantity in the pancreas hydrolyzes maltose into glucose

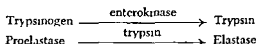
Lipase (steapsin) is the lipolytic enzyme of the pancreas It also works best at alkaline pH (optimum pH 8) It is easily destroyed by strong acid solutions or by trypsin and like amylase can be detected in the blood serum of normal individuals Pancreatic lipase is a powerful fat splitting enzyme changing insoluble neutral fats into fatty acids and glycerol It also has the ability to emulsify liquid fats Pancreatic lipase normally works in close cooperation with bile and the combination can digest fat 4 to 5 times more rapidly than the lipase alone The bile salts appear to increase the efficiency of the reaction by enhancing the activity of lipase possibly as a co ferment by emulsifying the fat and thus permitting more efficient digestion of fat in aqueous suspension and by forming water soluble complexes with fatty acids

As Thomas has pointed out the production of these enzymes by the pancreas involves two distinct processes (1) Synthesis within the gland and (2) Discharge of enzymes into the secretion

The first of these is believed to be a continuous process not subject to rapid change and so far as is known influenced primarily by the laws of chemical equilibrium and by those factors in the internal environment which determine the rate of cellular

tic fiber while E is proteolytic and digests the matrix of the elastic fiber and describes the action on elastic fiber as one in which E_1 loosens the outer layer of the fiber, which consists mainly of polysaccharide while E breaks the link between polysaccharide and protein matrix and carries both into solution

It has been shown that trypsin and chymotrypsin have no elastase activity (Balo and Banga Partridge and Davis Grant and Robbins) Grant and Robbins have also demonstrated that elastase is present in the normal pancreas in an inactive form which they have called Proelastase and that the latter is converted to elastase by trypsin They have presented the following scheme to demonstrate the activation of elastase



According to this concept then elastase is another proteolytic digestive enzyme also secreted by the acinar cells of the pancreas in an inactive form Grant and Robbins further have presented evidence that this enzyme is an endopeptidase with a specificity that includes elastin and possibly also acetyl L tyrosine ethyl ester Certain of these findings are also supported by the studies of Cohen *et al* who have shown that at least in the rat and guinea pig elastase is a digestive enzyme secreted by the acinar tissue of the pancreas and that any experimental procedure which causes a change in elastase concentration also elicits a similar change in pancreatic lipase concentration both in direction and degree They found elastase present in duodenal juice and could deplete the pancreas of this enzyme by pilocarpine administration Kokas *et al* and Lewis *et al* have also demonstrated the presence of elastase in the pancreatic juice of the dog

In our own laboratories Yu and Gertrude Blumenthal have found that a number of proteolytic enzymes may partially digest the elastic fiber but only elastase will produce extensive hydrolysis under physiologic conditions Yu has observed that this enzyme is specific for glutamic and aspartic acids phenylalanine and tyrosine Elastin is composed mainly of non polar amino acids except for small amounts of glutamic and aspartic acids hence the relative stability of elastin to digestion by enzymes

strated the presence of fibers with a similar function in the splanchnic nerves of dogs and Savich has been able to obtain secretion in some dogs by direct tetanization of the splanchnics Similarly Baxter has demonstrated the presence in rabbits of secretory fibers in the splanchnic nerves and Babkin in cats as well as in dogs A third type of nervous stimulus has been demonstrated by Kuntz and Richins who found reflex nervous pathways which do not traverse the central nervous system but run directly between the jejunum and pancreas of the cat and cause an inhibition of pancreatic secretion

Thomas has pointed out that Pavlov Gottlieb and more recently Babkin and others have reported that the secretory activity of the pancreas is greatly influenced by changes in the blood supply Conditions which decrease the blood flow through the gland diminish secretion while agents that increase the blood flow tend to augment secretory activity Local vasodilatation in the pancreas has been observed during active secretion Since the extrinsic nerves of the pancreas supply not only the secretory elements but also the pancreatic arteries a part of their influence may be attributed to changes in blood flow through the gland Similarly while the sympathetic nerves apparently do not exert an important influence over pancreatic secretion ephedrine seems to reduce pancreatic flow through its vasoconstrictor action

Hormonal control of pancreatic secretion has already been mentioned When HCl enters the duodenum from the stomach it combines with or acts upon a substance in duodenal epithelium to form secretin Secretin thus formed has been obtained in pure crystalline form by Agren This substance reaches the acinar cells of the pancreas via the blood stream where without the agency of nerve endings it provokes a profuse watery alkaline secretion relatively enzyme poor and rich in inorganic salts All the evidence indicates that secretin is a true hormone which acts independently of the nervous system This hormonal control is in a delicate balance since as soon as the alkaline pancreatic juice enters the duodenum it neutralizes the hydrochloric acid which has entered from the stomach If more acid comes from the latter more secretin is produced and there is more pancreatic secretion

metabolism in general It results in the elaboration and storage within the acinar cells of the characteristic pancreatic enzymes or their precursors It seems not be generally appreciated how ever that endocrine function may play an important role in their synthesis Thus Cohen *et al* have found that thiouracil ad ministration and also hypophysectomy results in a depletion of the elastase and lipase content of the pancreas of the rat and Baker *et al* have reported a similar depletion of pancreatic pro teinase after hypophysectomy Shafer and coworkers have also implicated the thyroid in the maintenance of normal proteolytic activity of the rat submaxillary gland

The process of secretion although ultimately dependent on synthesis is independently controlled Pavlov and coworkers showed that stimulation of the vagus resulted in a slow flow of thick concentrated juice especially rich in digestive ferments This effect of the vagus can be abolished with atropine while pilo carpin will stimulate a flow comparable to that produced by direct vagal stimulation According to Thomas the presence of inhibitory fibers was suggested in some of Pavlov s observations and was further demonstrated by Popielski who showed that stimulation of the peripheral vagus could inhibit the secretory activity of the pancreas produced by HCl in the intestine Popiel ski believed that certain branches of the vagi in the thorax and abdomen were purely inhibitory while others were purely ex citatory However Anrep was unable to confirm Popielski s re sults he found that all branches of the vagi that affected the pancreas contained both types of fibers He further noted that the pancreas increased in volume when the vagus nerves were stimulated provided there was inhibition of secretion but not if a free flow of juice occurred

In summing up vagus effects Thomas has concluded that evidently one effect is to augment the action of other stimuli but under certain circumstances these nerves are also capable of increasing pancreatic secretion independently Effects similar to those obtained with vagus stimulation may be produced by the administration of insulin (hypoglycemia) mecholyl chloride pilocarpine or prostigmine

In addition to vagus nerve control Kudrevezki has demon

b) *Hepatic Lipotropic Activity* A number of investigators (Fallis and Szylagyi Montgomery *et al* Dragstedt) have observed the development of massive enlargement of the liver from infiltration with fat following total pancreatectomy Since insulin has no effect on this process it is believed due to a deprivation of some substances elaborated by the acinar cells Dragstedt believes the substance to be a hormone which he calls Lipocaic On the other hand Montgomery *et al* have extracted another substance which they believe to be exocrine in origin and to be secreted with the pancreatic juice into the duodenum Both are called lipotropic factors A simpler substance choline is equally efficient in preventing such fatty infiltration Furthermore Fallis and Szylagyi believe that adequate diet alone provides sufficient lipotropic substance to prevent fatty change in the liver

c) *Electrolytes in the Pancreas* The pancreas also contains other substances of a critical nature a loss of which whether externally or internally requires replacement As Edmondson *et al* point out there is general agreement (Gamble and McIver Hart and Thomas Ball Comfort and Osterberg) that the total ionic concentration of pancreatic juice is about the same as serum and that the relative proportion of chloride and bicarbonate varies with the secretory activity of the gland In general the concentration of bicarbonate is considerably higher than that of serum and increases with the amount of pancreatic juice formed In dogs at least the bicarbonate may increase at the expense of almost all of the chloride ion and in man the bicarbonate may reach values of at least 130 mM/1 With the increase in bicarbonate there is of course an increase in pH in dogs the values are commonly from 8 8 3 and in man except under the influence of mecholyl or secretin usually not above 7 5 8 0 The concentration of sodium in pancreatic juice is 140 mM/1 and of potassium 5 mM/1 or also approximately the same as in blood The calcium ion concentration found by Ball in the pancreatic juice of dogs is 1 0 1 5 mM/1 corresponding roughly to the diffusible calcium in the serum The concentration of chloride is 40 mM/1 and of phosphate usually between 0 3 and 0 6 mM/1

Some insight into the normal rate of loss of such substances may be gained from studies with artificially produced pancreatic

until neutralization again occurs Harper and Raper believe that in addition to the effects of secretin there is another hormone, pancreozymin *which is similar to secretin in its mode of action* but which in the presence of secretin excites a flow rich in enzymes similar to that produced with vagus stimulation Greengard *et al* have separated a similar material from crude secretin and like secretin loses its activity on incubation with blood serum However Thomas has pointed out that there is as yet no evidence that pancreozymin is liberated into the blood stream from the living intestine and nothing to suggest the conditions under which it might function

There are in addition a group of diverse substances such as peptones proteoses acids fats fatty acids soaps and even water *which may act as secretogogues when they* are introduced into the duodenum Their mechanism of action is not entirely known but they appear to work independently of secretin The vagus nerve seems to be stimulated by the presence of fat and peptone in the duodenum and in general these substances produce a secretion with characteristics similar to those produced by vagus action Furthermore most of them are ineffective when the vagus is paralyzed

A clinical method which has been used for testing pancreatic function consists of passing a tube into the duodenum stimulating the pancreas with secretin and collecting and analyzing the pancreatic secretion It has been found that the maximum normal rate of secretion varies between 2 and 8 cc per minute and is usually attained in the first 10 20 minutes after stimulation the normal output per hour is 135 250 cc The normal bicarbonate output in one hour is 90 130 meq and the normal output of enzymes is diastase 300 1200 units per hour trypsin 20 40 units per hour and lipase 7000 14000 units per hour In each instance the output of these substances in normal individuals reaches a maximum in 20 40 minutes after stimulation and then declines (Cantarow and Trumper Dreiling and Hollander) Secretin administration will produce no increase in serum amylase in normal subjects but if substances capable of producing spasm of the sphincter of Oddi such as metholyl chloride urecholine or morphine sulfate are administered an increase occurs in the serum

combines stoicheiometrically with trypsin to form a trypsin inhibitor complex which is enzymatically inert Trypsin inhibitor also decreases the rate of transformation of trypsinogen to trypsin It may thus also inhibit the formation of chymotrypsin and probably also the conversion of proelastase to elastase However the amount of trypsin inhibitor in pancreatic juice is sufficient to *combine with only a small portion* of the trypsin in pancreatic juice In the intestinal lumen trypsin inhibitor is inactivated possibly by enterokinase (Kaiser and Grossman)

If such a substance is produced in some organ other than the pancreas and brought to the latter via the blood stream one may readily appreciate the importance of vascular integrity Ivy *et al* have concluded that the integrity of the blood supply is an important protective mechanism against the formation of peptic ulcer and Ivy and Gibbs have stated "It should be self evident that the pancreas will digest itself if it is deprived of all or much of its blood supply " The increased blood supply during secretory activity as previously noted may also serve to protect the pancreas when the release of enzymes is most marked

Martin has cited the literature on antibodies to enzymes such as trypsin which can inhibit their activity but as a protective mechanism one would have to assume a process of auto-antibody formation with the latter present in organs such as the pancreas which require protection such a mechanism has not been demonstrated

Martin also points out examples of naturally occurring inhibitors of proteolytic enzymes These have been found in Ascaris lumbricoides soybean and lima beans but similar substances have not been found in the human other than the inhibitors already mentioned Another mechanism of enzyme inhibition is the phenomenon of one ferment inhibiting another thus urease inhibits the action of trypsin but again this has not been demonstrated in the pancreas

Protection against autodigestion of the pancreas may also be afforded by certain dietary constituents although no definition of the latter has been accomplished The evidence for this exists in those clinical states of dietary deficiency and experimentally

fistulae Despite conclusive evidence that enzyme secretion by the pancreas is controlled separately from the secretion of fluid and electrolytes it is commonly believed that the acinar cells elaborate the latter as well as the former Thomas has pointed out that there is some evidence that fluid passes through the acinar cells when the pancreas is secreting even in the absence of specific enzymatic secretory stimuli Ball *et al* have injected bicarbonate containing radioactive carbon into the blood while collecting pancreatic juice The radioactivity of the juice attained a level of 4 5 times that of the blood corresponding to the ratio of total bicarbonate in juice and blood Thus the greatest part of the bicarbonate in the pancreatic juice comes from the blood Another electrolyte present in pancreatic secretion is sodium Montgomery *et al* found that radioactive sodium appeared in the juice within three minutes after it was injected into the blood after 15 minutes the concentration in the juice became equal to that in plasma and remained so throughout the experimental period

Thus with excessive loss of pancreatic secretion the blood chemistry reveals a diminution in both sodium bicarbonate and chloride ions The depletion of sodium reserves under such circumstances means a loss of extracellular fluid and hence marked dehydration Gamble has shown that the loss of chloride as well as sodium causes the blood CO to be maintained at near relatively normal levels in order that the sum of bicarbonate plus chloride may equal the total value for sodium

d) ***Protective Mechanisms Against Autodigestion*** In an organ which contains enzymes potentially capable particularly of auto proteolytic and lypolytic activity protective mechanisms must exist In the case of the proteolytic enzymes as has been pointed out the ferments are present in the pancreas in an inactive form and in the normal course of events become activated after they pass into the duodenum Furthermore Landsteiner (1900) showed that the albumin fraction of blood plasma contains a substance which protects the living cells of the body against tryptic activity Kunitz and Northrop have found anti tryptic substance present also in the pancreas and Kaiser and Grossman in secreted pancreatic juice This trypsin inhibitor

defense adjunct is the integrity of the vascular supply which not only is necessary to the viability of pancreatic cells but which also provides protease inhibitor and is necessary in providing substances for mucin production

produced dietary deficiencies noted in Part I in which low grade pancreatitis is found It is not clear whether the low protein high fat diets or the injection of ethionine and its effect of excluding the utilization of methionine act as a direct causal mechanism or effect a depletion of some protective factor In this connection too the increased susceptibility of alcoholics to acute pancreatitis may be due in part at least to an associated dietary deficiency

The presence in pancreatic secretion of mucin produced by the ductal epithelium may also constitute a protective device but in a limited area Mucin by coating the lining epithelium of the ducts may through a purely physical effect protect them However there is indirect evidence that such an effect may also be biochemical since a crystalline trypsin inhibitor has been isolated from ovomucoid by Lineweaver and Murray and their data show that amino groups of trypsin and carboxyl groups of ovomucoid are required for this inhibitory reaction Evidently the ducts particularly their distal portions require such an added protective mechanism because of the possible reflux of activated enzymes from the duodenum Flexner showed that the mucus content of the bile also protects the pancreas against enzymatic digestion

It is evident from the foregoing therefore, that mechanisms exist to prevent the activation of pancreatic proteases before they reach the intestine It is also obvious that pancreatitis may result when these mechanisms are overcome and digestion of pancreatic tissue initiated Balkin has presented evidence that when pancreatic juice gains access into the interstitial tissues activation of proteolytic enzymes readily occurs by a variety of means other than activation by enterokinase Such activation has been discussed more fully in the next section However Grossman believes that while the auto activation of pancreatic proteases can occur under a variety of circumstances it has not been rigidly proven that it occurs whenever pancreatic juice enters the interstitial tissues and special factors may be required to cause such activation At any rate it is evident that the potential attacking force in the main consists of the proteases trypsin chymotrypsin and elastase, as well as pancreatic lipase These are opposed by a defense consisting of inactive precursor enzymes enzyme inhibitors and possibly also by pancreatic mucin An important

latter category bile assumes particular importance and the significance of bile introduced into the pancreas has received attention below According to Elman edema with mild leucocytic infiltration usually subsides in a week to ten days leaving no significant residue and this may constitute the only alteration in "transient pancreatitis" On the other hand as pointed out previously this event may represent the first stage of more severe forms of pancreatitis

Presumably these agents act in the pancreas as they would in other organs by first increasing capillary permeability with resultant serous exudate Since necrosis is not a feature of this stage it is unlikely that severe damage to vascular walls occurs The release of H substances as postulated by Sir Thomas Lewis may constitute the mechanism by which edema and mild leucocytic infiltration is initiated or perhaps the liberation of leukotaxine as proposed by Menkin who believes this substance to be unrelated to histamine produces the inflow of fluid and leucocytes

If this first stage of the local reaction is sufficiently intense or prolonged leucocytic migration into the interstitial tissues of the pancreas becomes more pronounced Menkin would attribute this process not only to the liberation of leukotaxine" a thermostable crystalline nitrogenous substance with resulting lymphatic blockade by thrombi but in addition to the release of a leukocytosis promoting factor a thermolabile substance associated with the pseudo and euglobulin fractions of inflammatory exudates

Gibbs and Ivy have emphasized pancreatic ductal obstruction as a cause of edema They have observed that when a pressure of 30 cm of normal saline is maintained in the pancreatic ducts of dogs edema develops rapidly and that subsequent necrosis about small ducts occurs by pressure trauma In their studies demonstrating the reflux of diodrast into the pancreatic ducts Howell and Bergh observed that in all but four of the 50 patients exhibiting this phenomenon the pressure at which such reflux occurred was less than 30 cm of water In two of the four patients with a reflux pressure greater than this clinical symptoms of acute pancreatitis occurred Ivy and Gibbs believe that this

Chapter 11

PATHOLOGIC PHYSIOLOGY OF THE PANCREAS

The various precipitating causes discussed in Part I act essentially to initiate the disease process but the ensuing chain of reactions may take one of several courses Thus the subsequent alterations in the pancreas may proceed through the phases of predominantly serous exudation (edema) or predominantly purulent exudation (leucocytic infiltration) necrosis including fat necrosis and finally hemorrhage In some instances there may be progression only through the first phase with some variation in the intensity of leucocytic infiltration This is very likely the case in socalled transient pancreatitis If the exudative reaction is sufficiently intense it may serve to activate intrapancreatic enzymes with resultant necrosis and/or hemorrhage by mechanisms which have been described below In still other instances the reaction may progress through the first phase with extreme rapidity or not at all and in the latter event necrosis and/or hemorrhage may be the earliest process In part at least the character and intensity of the initiating causes may determine which of these courses the disease will take but in general there appears to be no relation between etiologic type and the direction or intensity of these phases

The important components of the pathologic lesions in acute pancreatitis then consist of (1) Edema and leucocytic infiltration of the interstitial tissues (2) Necrosis of parenchymatous structures (3) Fat necrosis (4) Vascular necrosis with resultant hemorrhage (5) Calcification of fat and parenchyma as well as the formation of intraductal calculi and (6) Fibrosis The pathologic physiology of these phenomena are discussed here while the pathologic anatomy has been presented in Part III

a) *Edema and Leucocytic Infiltration* Among the agents capable of producing edema when introduced into the pancreas are bacteria viruses their toxins or chemical irritants In the

that while normal bile in the intact gallbladder is harmless to the mucosa autolysis of the latter occurs rapidly if the organ is not immediately fixed following excision and he postulates the necessity of pre existing trauma or vasospasm to confer a state of susceptibility to necrosis in vivo

Bernard (1856) Flexner (1897) and Oser (1898) first noted the damaging effects of bile forcibly injected into the pancreatic duct system and Opie (1901 1910) also emphasized the role of bile in his development of the common channel thesis Flexner (1916) later concluded that the bile salts are the injurious agents while the colloids afford some protection Other workers (Hlava Flexner Polya Rich and Duff) have pointed out that these effects of bile are non specific and can also be produced with weak hydrochloric acid gastric juice intestinal secretion or commercial trypsin When bile is injected into the pancreatic ducts with sufficient force to produce rupture of the ducts hemorrhages acinar destruction and fat necrosis occur but Wangensteen *et al* and Thistlethwaite and Hill have found that bile injected directly into the substance of the gland results only in local edema Small quantities of bile introduced into the pancreatic ducts produce no lesions (Popper Archibald and Kaufman Coffey Wapshaw) Similarly artificially produced or natural communications which make possible the reflux of bile into the pancreas when coupled with stimulation of bile flow result only in slight or no acinar damage (Archibald Wangensteen *et al* Mann and Giordano Bisgard and Baker Tejerina Fotheringham) Clasen *et al* and McCaughan have reported that infected bile is more harmful than sterile bile but lesions of varying severity have been observed with sterile bile by Ireneus and by Baxter *et al* Characteristic of the effect of sterile bile is a leucocytic infiltration which may be accompanied by exudate formation while acinar loss is only patchy

As has been pointed out the high frequency of reflux of bile into the pancreas as demonstrated by cholangiographic studies constitutes evidence that there are many instances in which the mere presence of bile in the main pancreatic duct cannot do much if any harm Archibald has summed up the conditions which he believes are required for bile to have an injurious effect

increased ductal pressure in the presence of an actively secreting pancreas produces venous stasis and decreases blood flow, which may be a cause of the edema

Much has been made of the role of bile in the pathogenesis of acute pancreatitis and an evaluation of reports dealing with this factor seems to make its discussion most appropriate here In 1908 Chittenden and Albro stated The natural commingling of bile and pancreatic juice in the duodenum is strongly suggestive of a harmony of action and it might be reasonably assumed that in pancreatic proteolysis the presence of bile would be inimical" While as Wapshaw points out it is not known who first proposed the theory that bile is capable of initiating proteolysis almost general acceptance is given to the view that this is among the common predisposing causes of acute pancreatitis yet biochemists have long ceased to interest themselves in bile as an initiator of proteolytic activity Wapshaw has cited much of the older literature on which this misconception is based and concludes that it is doubtful that bile is an activator of the precursor of trypsin

On the other hand the essential irritating ability of bile is well appreciated by surgeons who work to prevent its escape into the peritoneal cavity Tatum (1916) demonstrated its cytolytic effect on blocks of fresh tissue in vitro and assumed there was some activator in bile which reacted with autolytic enzymes in the tissues Bradley and Taylor suggested that this cytolytic effect might be due to the solvent action of bile on cell lipids The injection of bile into the renal pelvis (Dragstedt *et al*) salivary duct (Sellards) or subcutaneous tissue (Rich and Duff) results in the formation of an inflammatory exudate but none of the specific components of acute pancreatitis Nevertheless certain workers consider bile capable of destroying pancreatic acinar tissue Tejerina Fotheringham has found that sodium taurocholate which is the principal salt in the bile of dog pig and ox is much more destructive than sodium glycocholate which is the principal bile salt in man rats cats and goats and Wapshaw points out that it may therefore be more than coincidence that in the former group of animals the common bile and pancreatic ducts open separately into the duodenum Wapshaw further notes

the direct action of some factor in inflammatory exudate or from the activation of trypsin by some factor in such exudate Furthermore certain of the initiating factors discussed in Part I may be capable of causing the entrance of pancreatic enzymes into the interstitial tissue Small amounts of pancreatic enzymes are normally present in this location apparently without harmful effects Pancreatic amylase lipase and probably also trypsin are normally present in the blood Grossman points out that these enzymes do not enter the blood by reabsorption from the pancreatic ducts or from the intestine after secretion but rather by their secretion from the end of acinar cells opposite the gland lumen They then traverse the interstitial spaces to blood vessels This process which represents a slight degree of endocrine secretion of predominantly exocrine products is accelerated in the presence of obstruction to the outflow of pancreatic juice In fact any increase in hydrostatic pressure constitutes an immediate cause of such an acceleration and explains such an effect by secretin which produces a secretion high in water and bicarbonate but low in enzymes Gibbs and Ivy have produced the same effect experimentally by increasing the intraductal pressure with saline Entrance into the interstitial tissues may also follow rupture of the ducts as in vomiting coughing or straining in the presence of ductal obstruction Necrosis of acini for whatever reason also results in a release of the total enzyme content of the destroyed cells into the interstitial tissues and their rapid absorption into the blood stream

The normal mode of conversion of trypsinogen to trypsin by enterokinase has been presented in the immediately preceding section Delezenne (1902) showed that enterokinase is not limited to the small intestine but is also present in lymph glands and Mellanby and Woolley (1913) brought forward evidence that enterokinase is present in small but definite amounts in practically every tissue of the body including fresh extracts of pancreas from animals Enterokinase is undoubtedly the triggering factor in those cases of pancreatitis in which there is regurgitation of duodenal juice into the pancreatic ducts a mechanism which has been particularly emphasized in those individuals with this disease in whom there are separate duodenal openings of

on the pancreas as follows (1) A change in the constitution of bile brought about either by infection or excess of bile salts, (2) Undue resistance of the sphincter of Oddi and (3) Abnormally high biliary pressure Wapshaw believes that there is no tangible evidence that infected bile is any more destructive than sterile bile and points out that factors which have to be taken into account are the virulence of the organisms their proteolytic activity and that of any leucocytes that may be present and finally, *a consideration of the bacteriostatic effect of the bile on the particular organism involved*

The essential irritating effect of bile is well demonstrated in the experiments of Rich and Duff in which this substance was injected subcutaneously and produced edema and mild inflammation Its presence in the interstitial tissues of the pancreas may under certain conditions lead to more severe reactions only because of the intrinsic characteristics of this organ Thus it would appear that if bile is introduced into the pancreatic ductal system with sufficient pressure to produce rupture so that the bile enters the interstitial tissues an inflammatory reaction may result due to the essential irritant quality of the bile salts On the other hand it has been pointed out that inflammatory exudate is capable of activating trypsin and necrosis from the proteolytic activity of the latter may occur as a secondary phenomenon As *Powers et al have shown only a small quantity of trypsin is* necessary to trigger the conversion of the inactive to the active form of this enzyme if a sufficient quantity of tryposinogen is stored in the pancreas A similar mechanism may obtain in the presence of inflammatory exudate from whatever cause and in addition such exudate may itself if sufficiently pronounced produce necrosis and further contribute to the conversion of trypsinogen to trypsin Menkin believes that inflammatory exudate contains a proteolytic substance which he has *called* necrosin which could have such an effect

b) *Parenchymatous Necrosis* Most workers attribute the remarkable self digestion of the parenchyma of the pancreas which constitutes acute pancreatic necrosis to the digestive action of trypsin as suggested by Polya (1908) However as has been pointed out necrosis may in the first instance result either from

the spleen when coupled with pancreatic ductal obstruction also results in acute hemorrhagic pancreatitis this finding is interpreted as evidence that necrosis of any organ causes a release into the circulation of trypsin which may then be carried to the pancreas where it triggers the conversion of trypsinogen to trypsin Presumably infarcts in the pancreas itself could serve as such a triggering mechanism and the resulting superimposed acute hemorrhagic pancreatitis might then mask a pre existing pancreatic infarct In this regard it is interesting that Wells has pointed out that there are kinases which occur in the pancreas itself during autolysis (necrosis) which can activate trypsinogen Thus in injury to acinar cells from any cause sufficient to produce cell death the dead and injured cells are digested by the pancreatic juice which is thus further activated

While infarction of various organs may thus initiate tryptic activity within the pancreas it may not be valid to assume that this can only be due to a release of trypsin in light of the observations that enterokinase is also present in small amounts in practically every tissue of the body and could act in similar fashion These observations have additional significance in that they point out that pancreatic ductal obstruction alone serves only to cause an accumulation of trypsinogen and that additional mechanisms are required to activate the latter They may also serve to point up the significance of the high incidence of infarction noted in the idiopathic group as presented in Part I

There are also many other circumstances which may cause a spontaneous" activation of trypsin which deserve attention Spontaneous activation was first reported by Heidenhain (1878) and subsequently reported by Babkin (1904) Savich (1909) Mellanby and Woolley (1913) Waldschmidt Leitz (1924) and others Northrop believed that the biochemical mechanism by which trypsinogen was converted to trypsin consisted of an autocatalytic reaction in which the transformation resulted from an internal rearrangement in the molecular structure which consisted presumably in the hydrolysis of a polypeptide ring The socalled vagus juice evoked on stimulation of that nerve or by the administration of certain drugs previously noted may spontaneously evoke this change (Savich Anrep) and some investi

the pancreatic and common bile ducts with the former lacking the protective factor of a sphincter But this mechanism must obtain only rarely because of the rarity of acute pancreatitis in patients with small bowel obstruction

Despite numerous older reports indicating that bile does not activate trypsin the more recent studies of Elliott *et al* show that under certain conditions bile is able to effect the conversion of trypsinogen to trypsin These investigators have again confirmed the observations that the pancreatic secretory pressure is normally higher than the pressure obtained in the common bile duct so that pancreatic secretions enter the biliary tree following common channel obstruction Under pressures known to occur in the distended biliary tree the pancreas resists infiltration by normal bile but if a mixture of bile and enzyme rich pancreatic juice is permitted the pancreatic ducts will accept a small amount of this mixture However if the latter is further permitted to incubate for 12 48 hours the pancreas accepts it in large quantities at low pressures and acute hemorrhagic pancreatitis occurs The reason for this increased acceptance is not clear and the authors state that it is apparently not due to the decreased viscosity of the bile which results from tryptic digestion of bile mucin On the other hand viscosity of the mixture is progressively lost indicating a deterioration of mucin which may enhance whatever effects bile salts may have in this interaction (Flexner) Moreover the incubated mixture may have an injurious effect on ductal epithelium not produced by a fresh mixture thus permitting infiltration into the pancreas Equal parts of bile and pancreatic juice appear to constitute the optimum proportions for the production of pancreatitis

Another mechanism is suggested by the studies of Powers Brown and Stein These investigators have found that the injection of small amounts of trypsin into the pancreatico duodenal artery of dogs results in only small foci of hemorrhage but that if trypsinogen is caused to accumulate in the pancreas by producing ductal obstruction then small quantities of trypsin so introduced can trigger the conversion of trypsinogen to trypsin and widespread pancreatic hemorrhage occurs They have also observed that artificially produced infarcts of other organs such as

will produce all of the components of the hemorrhagic necrosis in subcutaneous tissue when injected into that site This observation also suggests that the disseminated extrapancreatic foci which occur in acute pancreatitis may be the result of dissemination of activated pancreatic juice

Several investigators attribute necrosis in the pancreas to agents other than trypsin Thus Hosie and Ziffren have postulated an intermediate mechanism with the escape of pancreatic juice into the interstitial tissues by any of the various mechanisms discussed in Part I pancreatic collagenase begins to act on the surrounding tissues liberating another factor which may then activate the conversion of trypsinogen into trypsin They point out that collagenase requires no activator and in this regard is similar to amylase and lipase It is destroyed by heat in contrast to trypsin Nemir and Drabkin believe that a vascular component is the principal factor in the onset of necrotizing pancreatitis permitting plasma and red cells to come in contact with pancreatic juice They have shown that these components of blood interact with the pancreatic juice to form a highly toxic substance (not activated trypsin) capable of producing necrosis after which the process is self perpetuating and trypsin may then also play a role

Reid *et al* have also stressed the importance of loss of vascular integrity as the precipitating factor causing certain changes in cells which permit the action of enzymes other than trypsin These authors hold that the mechanism of necrosis of the pancreas cannot be due to trypsin since no mammalian enzyme can seriously disturb much less digest a healthy well preserved cell and that integrity of the cell membrane since it is not protein is not likely to be altered by a proteolytic enzyme Their conclusion as to the nature of the cell membrane appears to be open to question since the studies of Schmitt *et al* indicate that the cell membrane is probably formed of parallel leaflets of proteins separated by a double layer of lipids Reid *et al* have observed that pancreatic homogenates markedly depress the oxygen uptake of tissues of other organs while homogenates of no other organs so far studied have this capacity This effect is attributed to enzymic inducers which normally synthesize the digestive enzymes of the pancreas and not to the latter enzymes themselves This conclu

gators believe that a heavy meal may have the same effect (Gulleke Rich and Duff)

The pH of the pancreatic juice may also be an influencing factor in spontaneous activation Heidenhain (1883) noted that the addition of an alkali retarded auto activation while an acid facilitated the process and Mellanby and Woolley (1913) believed that any agent which neutralizes the alkalinity of pancreatic juice without destroying trypsinogen produces rapid activation other workers believed that this was the mechanism by which vagus juice and pilocarpine accomplished auto-activation (Kudrevezski Savich De Zilwa) Thus it appears that normal alkalinity of the pancreatic juice may be a safeguard against spontaneous activation

The importance of such spontaneous activation as a potential source of danger is emphasized by reports that prolonged stimulation with parasympathomimetic drugs may result in acute pancreatitis The administration of mecholyl results in acute inflammation which may progress to focal hemorrhage fat necrosis and degenerative changes in acinar cells (Tucker Wener *et al*) There is suggestive evidence that a dual mechanism may obtain in this regard Anrep has described some contraction of pancreatic ducts following vagal stimulation and Kitakoji has observed that some choline derivatives may cause the sphincter of Oddi to contract This may constitute a mechanism whereby trypsinogen is caused to accumulate in the pancreas so that when auto activation occurs there may result a sufficient concentration of trypsin to produce pancreatic necrosis as suggested by the studies of Powers *et al*

As previously mentioned calcium may also bring about the conversion of trypsinogen to trypsin but this appears to be a slow process requiring about seven hours (Delezenne Effront) Mellanby and Woolley believe that calcium does not initiate but only accelerates trypsin production The role of calcium therefore remains in doubt

Again the singularly peculiar characteristics of this reaction have been demonstrated by Rich and Duff, who showed that activated pancreatic juice collected from the pancreatic duct

possible that the depression in oxygen uptake is due to a summation of effects of the numerous enzymes synthesized in the pancreas, each with its own specificity. Such a summation would not be expected to be analagous to the arithmetic sum of the activity of each individual enzyme since the action of one may expose bonds otherwise inaccessible to other enzymes upon which certain of the latter may then act.

Until such time as there is direct proof of cytolytic effects of these enzyme inducers one must reserve judgment regarding the concept proposed by Reid *et al*. Furthermore, while such substances might produce initial degenerative changes in cells leaving them susceptible to digestion by proteolytic enzymes of the pancreas, it appears that in the final analysis pancreatic necrosis is due to a summation of effects of the digestive enzymes of that organ. If one were to attribute to these inducers the sole potential for producing necrotic changes in the pancreas, it would also be necessary to postulate that they enter the circulation in order to account for the dissemination of fat necrosis, unless it is assumed that the latter is solely an embolic phenomenon.

c) ***Fat Necrosis.*** Wells has reviewed the older literature with regard to fat necrosis and little has been added to our knowledge since these early studies. Thus, Langerhans made the first studies which established the fact that the fat of the cells is split into its components and that the fatty acids combine, at least in part, with calcium. Dettmer later showed that the fat splitting was due to the lipase of the pancreatic juice and Flexner demonstrated lipase in foci of fat necrosis. Klotz later confirmed these observations.

Injury to the fat cell with a release of neutral fats does not appear to be a necessary prerequisite to fat necrosis since, as pointed out in Part I, the latter may occur at sites distant from the pancreas, presumably as an effect of increased circulating lipase, unless it is assumed that circulating proteolytic enzymes first injure the cell membrane and cause a release of neutral fat. In any event the latter is acted upon by lipase and broken down to fatty acid and glycerol. Glycerol is water soluble and is carried away by the lymphatics while the fatty acid combines

sion is drawn largely from the observation that pancreatic homogenates continue to exert the depression in oxygen uptake even after trypsin and chymotrypsin have been inactivated but it fails to take into account that there are other pancreatic enzymes such as elastase peptidases nucleases collagenase etc previously listed for which activity was not tested

These authors postulate that when vascular function is impaired substrate is excluded from the pancreatic cells which normally possess the greatest protein synthesizing capacity of any structure in the body anabolic enzymes then exert a catabolic effect because proteolytic activity is merely a reversal of the direction of equilibrium from that of a protein synthesis as suggested by Bergmann However this does not appear to be a universally applicable principal since Monod has shown that in certain bacteria at least (1) induced enzyme formation involves the complete *de novo* synthesis of the enzyme protein molecule from its elements or elementary building blocks (amino acids) (2) the induced synthetic process is virtually irreversible and the finished enzyme molecule is not removed at a measurable rate (i e is not in a dynamic state within the cells) (3) the process of enzyme induction is independent of enzyme action and (4) the inducer is not consumed in induction The inducer acts as a catalyst only in the sense that one molecule of inducer may activate the synthesis of more than one enzyme molecule Within the scope of the concept propounded by Reid *et al* it would thus appear that the substances responsible for the synthesis of trypsinogen chymotrypsinogen etc are essentially inducers

Reid *et al* postulate that in the living situation the initial steps in pancreatic necrosis consist of a vascular lesion which causes not only a diminution in substrate upon which these enzymes (inducers) may act but also a loss of cell membrane continuity disorganization of cell architecture and extrusion of those intracellular enzymes which now act catabolically upon the cell contents as well as the surrounding inadequately irrigated cells to produce the final picture of total necrosis Direct proof appears to be actually lacking in these investigations for a reversal of activity of these enzymes (inducers) and it is equally

nothing comparable to this phenomenon in any other place in the body. Rich and Duff attributed this to the action of trypsin but in light of more recent work it appears unlikely that this proteolytic enzyme is capable of totally digesting the walls of arteries.

In unrelated studies carried out in connection with the rupture of Berry aneurysms of the cerebral arteries Forbus showed that while the congenital defect of the muscular coat of these arteries at their point of bifurcation might indeed account for their weakness and the aneurysm formation rupture in the final analysis was due to the development of breaks within the elastic lamella. The latter is the structural component of arteries with the greatest tensile strength and rupture is unlikely to occur without a break in its continuity.

As Blumenthal has shown such a break may occur in one or both of two ways (1) either by gradual wear and tear resulting from the prolonged mechanical effects of intravascular pressure or degeneration resulting from inflammatory processes or (2) enzymatic digestion. The first of these is a prolonged gradual process and may be the cause of pancreatic infarction or pancreatic artery rupture. The second can occur acutely and suddenly as a result of the action of pancreatic elastase as noted in the previous section of Part II. Since elastase was unknown at the time of the studies of Rich and Duff it is not surprising that they attributed this effect solely to the action of trypsin. As to the experiments of Rich and Duff with the injection of pancreatic juice or trypsin into the subcutaneous tissue with the production of hemorrhage the results might be accounted for in two ways: their pancreatic juice in all likelihood contained active elastase since the latter appears to be another proteolytic digestive enzyme of the pancreas and secondly one cannot now assess the purity of some of their trypsin preparations which may have contained elastase. Finally their results in experiments with crystalline trypsin may have been due to multiple capillary hemorrhages rather than rupture of larger arteries in which case trypsin could account for the lesions since such small vessels lack elastic fibers. Or the trypsin could have activated the proelastase in the pancreas.

with calcium to produce soaps which are deposited at the sites of this reaction Subsequently inorganic calcium salts appear at *these sites with disappearance of fatty acid but the mechanism* of this reaction is not known Hence as Wells has pointed out the fat splitting is not the cause of the necrosis but occurs subsequent to the necrosis

Incidentally Wells has also observed that in socalled fat necrosis from causes unrelated to pancreatitis the lipase normally contained within fat tissue does not cause the changes just described He suggests that the combining of newly split fatty acids with the alkali of the pancreatic juice may be responsible for the formation of the large quantities of soaps found in fat necrosis associated with acute pancreatitis Otherwise it might be expected that the lipase would produce only an equilibrium and this seems to be the case when most of the substance is neutral fat Thus he was able to convert fat necrosis of other types into that characteristic of pancreatic disease by the addition of strong alkali

As Wells further points out this fat necrosis is in itself not dangerous since there is no evidence that sufficient quantities of soaps (which are toxic) are absorbed from the necrotic areas to cause appreciable intoxication about 85 per cent are precipitated as insoluble calcium soaps

Lipase appears to be secreted in the active form by acinar *cells and Rich and Duff have noted that juice of enzyme* concentration too weak to produce hemorrhagic necrosis even when the enzymes are activated will when injected into subcutaneous tissue produce fat necrosis In part at least this may also be due to the fact that the mechanisms protective against the digestion of tissue by the proteolytic enzymes are more effective than those which may be present to protect against lipolysis

d) *Vascular Necrosis* Since the important contribution of Rich and Duff it has become generally accepted that the hemorrhagic component of the lesion of acute pancreatitis which may convert a mild *or moderate disease process into a severe one is the result* of enzymatic digestion of vascular tissues with their subsequent rupture Ivy and Gibbs have remarked that there is

As regards the formation of ductal calculi it has been pointed out that calcium is precipitated within those tissues which are locally alkaline as a result of their acid secretion conversely it has been suggested that calcium is not precipitated in those tissues which are locally acid when producing alkaline secretions but rather in the ductal systems of such organs This is supported by the observations that such calculi are composed of calcium carbonate and phosphate (Askanazy Martin and Canseco) Edmondson *et al* have pointed out that the occurrence of calculi of various sizes in the pancreatic ducts is in accord with the theory that precipitation is due primarily to the supersaturation of pancreatic juice with calcium carbonate Under normal conditions the pancreatic juice shows such supersaturation for the ion concentration product of CaCO will reach values of at least 1×10^{4} whereas the solubility product is about 5×10 However this is at variance with the relatively infrequent occurrence of pancreatic ductal lithiasis and either some unknown factor operates to prevent the precipitation of this calcium or small calculi are formed and passed into the duodenum with considerably greater frequency than is generally realized We would not agree with Edmondson *et al* that debris in dilated ducts contributes significantly to this process in acute pancreatitis since in our experience such debris is common in the inflamed as well as non inflamed pancreas

The formation of calculi in the pancreas however may not be dependent solely upon considerations of solubility product of calcium salts since the latter apply only to solution in water Schade has described conditions necessary for stone formation in the urinary tract which may also obtain in the pancreatic ducts these include not only the precipitation of crystals from a saturated solution but also the effects of the medium in which crystallization occurs The solvent in which the calcium salts are found in the pancreas may contain an organic colloidal material such as mucin from which the nuclei of minute calculi are formed On the other hand Lichtwitz has concluded that the ability of the salts in the urine to form stones is related to the presence of certain colloids which prevent precipitation and agglutination of salts and other colloids Physical factors enter into

In massive acute hemorrhagic pancreatitis however hemorrhage occurs in such quantity that it could only be accounted for on the basis of rupture of larger vessels and it now appears that complete dissolution of the wall could only be accomplished by a combination of enzymes Trypsin and collagenase can account for the destruction of muscle and connective tissue structures but destruction of the remaining barrier the elastic lamellae, would depend upon the action of elastase Furthermore if one assumes the existence of an intact external elastic lamella then the latter could conceivably exclude trypsin from the inner components of the vascular wall Elastase therefore appears to assume considerable importance in the pathogenesis of the acute hemorrhagic form of pancreatitis and further consideration has been given this matter in Part III

e) ***Calcification*** Two distinct types of calcification occur in the pancreas in association with acute pancreatitis (1) Calcification of foci of fat and parenchymatous necrosis and (2) The formation of intraductal calculi In large part calcification of both types appears to be facilitated by the alkaline medium afforded by the pancreas (Askanazy Hanes Wells) but other than in this regard there appears to be no relation between these two forms of calcification

As regards the first of these eventual calcification of necrotic tissue is a well recognized pathologic phenomenon but calcification of necrotic fat appears to be somewhat different since here calcium deposition is relatively rapid and the process may progress to eventual resorption of the calcific deposits Thus Wells has noted that experimentally produced foci of fat necrosis with calcification may disappear as early as eleven days after their formation and Wells and Mitchell have confirmed this observation Even in the situation in which pancreatitis is associated with hyperparathyroidism some investigators believe that calcification is preceded by local necrosis (Ackman and Ross Cantarow *et al*) and this is supported by the experimental observation that focal necrosis of the pancreas as well as of other organs can be produced with overdosage of parathormone (Hueper McJunkin *et al*)

ly if the latter is of the recurrent variety and that the calculi develop as a result of the hyperparathyroid state while in other instances hyperparathyroidism may be of the primary variety leading to the formation of ductal calculi within the pancreas which initiate the pancreatitis

f) *Fibrosis* It is not within the scope of this subject to enter into a discussion of the factors in inflammatory and necrotic tissue which stimulate fibroblastic proliferation and the eventual formation of scar tissue Such organization appears to be in no way different in the pancreas from that in any other organ In general however it is well to point out that since such scar tissue does not seem to develop in transient pancreatitis it would appear that the disease must progress to the point of necrosis of fat and parenchymatous elements in order for fibrous tissue to occur The latter through its characteristic of undergoing contraction after fibroblasts are replaced by collagen may then pinch off ductal structures to produce intrapancreatic ductal obstruction and in this way sensitize the pancreas to subsequent attacks of pancreatitis

g) *Pancreatic Function in Pancreatitis* The basic technique of the secretin test previously described has been used to evaluate organ function in pancreatic disease However the procedure cannot be performed readily on the patient sick with acute pancreatitis so that much of the information available is referable to residual sequelae and complication Agren and Lagerlof as well as Abbott and Rawson have developed special tubes for the separate collection of gastric and duodenal juice Substances which have been used to stimulate pancreatic secretion include secretin (Comfort and Osterberg Dreiling) metacholine bromide (Comfort and Osterberg) and bethanical chloride (Kyle *et al*)

In most cases immediately following mild pancreatitis the results of the secretin test are normal However Lagerlof reported that in 32 patients with pancreatitis 21 secreted a normal amount of bicarbonate when given secretin but only 12 produced a normal concentration of enzyme In a similar study Friedman and Snape found some patients whose pancreatic juice was

these processes Electrical charges around colloidal particles act to prevent their collection into larger aggregates Another important factor in preventing precipitation and agglutination of colloids and crystalloids is that *sedimentation of finely divided material may* be almost entirely counteracted by the Brownian motion of the colloidal particles Calculus formation thus probably *results from an imbalance of colloids and crystalloids but such* considerations with regard to the formation of calculi in the pancreatic ducts appear to have been neglected The formation of *such stones may be at least as much dependent upon alterations* in the colloidal nature of the pancreatic secretion as on the solubility product of the calcium salts The observations of Edmondson *et al* *showing that the solubility product for calcium salts is* commonly exceeded in pancreatic secretion while the formation of calculi is relatively infrequent would tend to support a dependency upon *such alterations in the colloidal state of the pan*creatic juice

In hyperparathyroidism with pancreatitis as discussed in Part I it is not certain whether hyperparathyroidism is the primary condition producing pancreatic lithiasis with obstruction to initiate the pancreatitis or the latter initiates the hyperparathyroidism As noted by Edmondson and Berne hypocalcemia is frequently found in pancreatitis as a result of the mobilization of calcium in foci of necrosis in the pancreas and secondary hyperparathyroidism is a well recognized condition believed to arise from the stimulus of low serum calcium (Hastings and Huggins Patt and Luckhardt Sinclair Stoerck and Carnes Talbot *et al*) In long standing relapsing pancreatitis with lithiasis serum calcium levels are also frequently depressed presumably as a result of the fatty diarrhea and failure of absorption of fat soluble vitamins This could also act to stimulate parathyroid activity and the formation of ductal calculi would again constitute a secondary phenomenon and not of causal significance in initiating the pancreatitis On the other hand when the hyperaparathyroidism *is* primary as Cope *et al* point out the acute pancreatitis may lower the serum calcium sufficiently to obscure the hyperparathyroid state It is therefore conceiv*able that in some instances hyper*parathyroidism may develop secondary to pancreatitis particular

stools of patients with pancreatic insufficiency is attributed to the breakdown of neutral fat in the colon by bacteria (Nothman) The absence of pancreatic proteolytic enzymes is manifested by the presence of undigested muscle fibers in the feces (creator rhea) which can be identified by their typical cross and longitudinal striations and may be brought out by placing patients on a diet of large amounts of raw chopped beef or ham Muscle fibers can also be broken down by the action of intestinal bacteria (Nothman) and creatorrhea may be missed if the fecal material remains in the colon for a long time The presence of starch granules (amylorrhea) is not considered significant

Machella has detailed the technique for the quantitative determination of fat and nitrogen content of feces on a fixed dietary intake of fat protein and carbohydrate The Schmidt diet (Johnstone) utilized in this procedure contains 105 gm protein 135 gm of fat and 180 gm of carbohydrate In normal persons up to 6 per cent of the fat and up to 8 per cent of the nitrogen ingested are excreted in the feces In complete obstruction of the pancreatic ducts about 60 per cent of the ingested fat and about 50 per cent of the ingested nitrogen may be recovered from the feces Such increases may occur also in sprue in which however the larger proportion consists of free and combined fatty acids rather than neutral fat and an increased amount of fat in the stools can also occur in common duct obstruction when intestinal transport is very rapid Fecal nitrogen is usually normal in common duct obstruction and in sprue but greatly increased (azotorrhea) in pancreatic insufficiency Riggs and Stadie have used orally administered protein labeled with I^{131} to demonstrate diminished hydrolysis of protein in chronic pancreatitis

While these clinical observations give only information as to pancreatic function after the acute attack has subsided some information regarding the mechanisms by which these changes occur is available Jordan and Hallenbeck have found that when the hydrostatic pressure against which the pancreas is secreting is gradually elevated secretion is not suppressed until near maximal secreting pressure is reached From this it may be assumed that with ductal obstruction the intraductal pressure will rise to the maximal secretory pressure (30 40 cm of water) and will re

wholly without tryptic activity but who secreted a normal amount of alkaline fluid in response to secretin Dreiling studied 48 patients with acute pancreatitis and found a slightly diminished bicarbonate and amylase concentration of the pancreatic secretion in 20 while the concentrations of these substances in the remaining 28 were normal

When abnormal secretion is found it has no definite characteristics which aid in diagnosis A test giving negative results may simply indicate that pancreatic function has returned to normal by the time the test is performed Positive reactions are of importance because they indicate persistence of pancreatic damage

In obstructive disease of the pancreas the secretin test has revealed decreased values for volume bicarbonate and enzymes In mild forms of acute and recurrent pancreatitis the decrease in amylase and lipase secretion usually precedes the decrease in trypsin and the volume and bicarbonate output is less easily disturbed On the other hand with obstruction of the main pancreatic duct or marked diminution in the mass of functioning pancreatic tissue there is a diminished output without such dissociation Certain gross microscopic and biochemical changes in feces may also furnish evidence of abnormal pancreatic function Thus the presence of undigested food may supply evidence of inadequacy of the external secretion of the pancreas In marked pancreatic insufficiency the stool is bulky glistening pale and rancid The pallid appearance is due to the presence of pus, fatty acids and soaps Such stools usually have the consistency of thick butter and will float near the surface of the water Steatorrhea the term applied to feces consisting of masses of fat resembling butter or cream when patients are placed on a high fat diet is highly suggestive of pancreatic disease

Microscopic examination of stools in pancreatic achylia also usually reveals large quantities of fat in the neutral form Sudan III added to such stools stains neutral fat red and free fatty acid orange while soaps remain unstained unless the fatty acids are liberated by the addition of a drop of 30 per cent acetic acid and heating to the boiling point The presence of fatty acids in the

Chapter 12

PATHOLOGIC PHYSIOLOGY OF BODY FLUIDS AND ORGANS OTHER THAN THE PANCREAS

a) *Hematologic Alterations* Two hematologic findings frequently observed in acute pancreatitis are anemia and leucocytosis The anemia is usually attributed to the hemorrhagic component of the acute pancreatitis and if severe may indicate hemorrhage into the peritoneal cavity Leucocytosis above 10 000 occurs frequently and it may rise to as high as 30 000 (Dozzi and Bockus Richman Fallis and Plain Lewison Roberts *et al* Healey *et al*) Richman has reported that in 75 per cent of his 58 cases leucocyte counts were over 10 000 and in the remaining 25 per cent they ranged between 20 000 and 30 000 According to Bockus *et al* the exception to this generalization occurs in the alcoholic group where 60 per cent of patients show leucocyte counts of 10 000 or less

Herfort has noted a decrease in lymphocytes as a regular finding in his study of 38 patients with acute pancreatic necrosis the degree of lymphopenia paralleled the severity of the disease and clinical recovery was accompanied by a rebound with mild lymphocytosis

In the present series of 163 cases of acute pancreatitis 112 or about 68 per cent showed leucocyte counts of 10 000 or over The highest count was 60 000 in a patient with a leukemoid reaction and the lowest was a normal count of 5 000 In 16 patients or approximately 10 per cent the proportion of lymphocytes in the differential count was less than 10 per cent but the absolute number of circulating lymphocytes was not abnormally low since all of these patients exhibited a leucocytosis with a high proportion of immature leucocytes to account for the relative diminution in lymphocytes In many instances particularly where the pancreatitis was either a contributing or incidental disease

main at this level until the continued exposure to this pressure causes the gland to lose its ability to secrete Complete obstruction of the ducts in rabbits leads to a rapid decrease in the response to secretin and pancreozymin at the end of four days these responses are reduced to about 20 per cent of control values following which there is a slower rate of decline with enzyme response abating more rapidly than volume response (Wang *et al*)

After forcible injection of bile into the pancreatic ducts of dogs (Hallenbeck *et al*) impairment of secretion is maximal immediately and involves both volume and enzyme production With moderate damage recovery occurs over a period of weeks but with severe damage may be slow and incomplete or absent With ethionine induced pancreatitis impairment of secretion is maximal at the time when serum enzyme levels show a transient rise In this form of pancreatitis enzyme secretion is depressed to a somewhat greater extent than is volume secretion With moderate damage again complete recovery may occur when ethionine is discontinued

Thus with these several types of experimental pancreatitis there is impairment of pancreatic secretion with a tendency for greater suppression of enzyme production than of volume As Grossman points out to some extent this decreased functional capacity of the injured pancreas may have a protective effect in that it tends to limit further damage

of the coagulation time In further support are the observations of Lasher and McCabe who noted a slight shortening of the clotting time and an initial decrease in prothrombin time in experimental acute pancreatitis in dogs of Abrams who reported similar phenomena in human cases and Shinowara *et al* who demonstrated a consistently marked thromboplastic plasma component in patients with acute pancreatitis and in dogs with experimental pancreatitis which they believe increases the coagulability of the blood

The literature on the effect of trypsin and tryptic enzymes and their antagonists has been reviewed by Eagle and Harris Ferguson and Erickson and by Tagnon The latter has emphasized the fact that small amounts of trypsin in vivo will promote the coagulation of blood by the conversion of prothrombin to thrombin whereas larger amounts produce shock with prolongation of the clotting time due to the consumption of prothrombin and fibrinogen secondary to massive intravascular clotting Heparin and heparinoid substances block the coagulant action of trypsin Shingleton *et al* have suggested that in chronic (recurrent) pancreatitis there is ductal obstruction and therefore during pancreatic stimulation trypsin enters the circulation and is responsible for the prolonged coagulation time Their negative results were obtained in patients with far advanced disease and this may be interpreted as indicating that in the latter there was a marked loss in the ability of the pancreas to form trypsin Other contradictory results noted above may be related to variations in the level of serum tryptic activity which depends upon the time elapsed following the onset of acute pancreatitis Such variations are discussed more fully in the sections on circulating enzymes

Innerfield *et al* have measured the plasma antithrombin levels in patients with pancreatic disease and have found no elevated antithrombin titer in recurrent pancreatitis pancreatic cysts fibrocystic disease and in carcinoma of the pancreas They have found an elevated plasma antithrombin level in 50 of the 55 cases with proved acute pancreatitis which exemplified a direct quantitative variation between hypertrypsinemia and plasma antithrombin In certain of the patients with chronic relapsing pancreatitis there are also elevated antithrombin titers and in some

and not the primary illness leucocytosis could be attributed to pathologic processes in organs other than the pancreas On the other hand in three of the 14 cases in which pancreatitis was the primary disease process (18 per cent) there was no evidence of leucocytosis

Roberts *et al* have reported an increased sedimentation rate in five of seven patients with acute pancreatitis In the present series sedimentation rate was determined in 132 of the 163 cases and was increased in 82 (62 per cent)

Zollinger *et al* and also Howard have emphasized a decrease in circulating blood volume and hemoconcentration a change usually associated with shock which Zollinger *et al* observed in over 50 per cent of their cases Shock was present in all of the cases in the present series in which pancreatitis was considered the primary cause of death but circulating blood volume deter minations were not recorded in any of the cases

Alterations in blood coagulation have also been noted in acute pancreatitis Hypothrombinemia is a fairly common occurrence (Richman Roberts *et al* Arkin Michella and others) and this is usually attributed to impaired liver function The literature dealing with alterations in blood coagulability in acute pancrea titis has been reviewed by several investigators (Shingleton *et al* Shinowara *et al* Innerfield *et al*) It has been pointed out that the widely disseminated venous thrombosis accompanying car cinoma of the pancreas has been attributed to the release of trypsin into the systemic circulation via the portal circulation resulting from obstruction of the pancreatic ducts This is sup ported by the observation of Boldyreff and Boldyreff Turcatti as well as Lundberg that the clotting time is prolonged in pan createctomized dogs and by the studies of Ferrari and Cortese, who observed a similar prolongation in blood coagulation with external pancreatic fistulae On the other hand Ferrari and Cortese as well as Hiruma have reported that pancreatic duct ligation also results in a prolonged clotting time Nevertheless both reports concluded that the influence of the pancreas on blood coagulation was via the external pancreatic secretion and that upon removal of these secretions there was a prolongation

down of pancreatic protoplasm can account for a mobilization of potassium into the blood and its excretion in the urine with resultant hyperpotassemia as noted in five of the fatal cases in their series secondary to pancreatic tissue breakdown and also to renal failure Roberts *et al* have reported two cases with serum potassium levels of 10 5 and 26 7 mg per cent the latter in a patient with a plasma chloride value of 462 mg per cent and a CO combining power of 86 2 volume per cent

Edmondson *et al* have also found low magnesium levels in four patients during the first four days of illness which lasted for 24 to 48 hours There appeared to be no correlation between the low magnesium values and the occurrence of a low serum calcium or potassium Low sodium values were observed in eight patients and there was no correlation with the severity of the disease or with the changes in other electrolytes Carbon dioxide values were not appreciably changed On the other hand Roberts *et al* measured the CO combining power in 11 cases of acute pancreatitis and in two of these found combining capacities of 73 and 86 2 vols per cent the chloride levels were 404 and 462 mg per 100 ml of plasma in the same specimen of blood In three other patients the CO combining power was greater than 70 volumes per cent and in six it was less than 40 volumes per cent

It is quite evident from a perusal of the literature that alterations in serum calcium concentration has received considerably more attention than that of any of the other electrolytes According to Berk hypocalcemia occurs during the first week of the disease and may last for from two to three weeks up to 70 per cent of the cases of acute pancreatitis may show this change It usually develops within 24 to 72 hours after the onset of an attack and the decrease is usually of slight degree (8 8 5 mg per cent) However values below 7 mg per cent accompanied by tetany *have been recorded* (*Gaster et al* Becker *Lepp and Hubbard* Amano and Murata Bertelsmann Cibert and Plauchu Trevor and Brown Gambill *et al* Hayes Bockus *et al* Edmondson and Fields Edmondson and Berne) Clinical improvement may precede by several days the return of serum calcium to normal levels Edmondson and Berne have attributed this change to the rapid mobilization of calcium from the blood serum into the areas of

of the cases with this disease and normal titers the latter can be elevated by the administration of urocholine or prostigmine Markedly elevated antithrombin titers also occur in some cases of fibrocystic disease indicating that there may be a stage of enzymatically induced interstitial pancreatitis with this condition Moseley *et al* have found the antithrombin test positive in 11 of 13 patients with acute pancreatitis while the best results were obtained early in the disease the test remained positive in many patients for at least 36 hours On the other hand Dreiling and coworkers have found elevations in the antithrombin titer in six of 49 patients with no clinical or laboratory evidence of pancreatic disease

In animal experiments Innerfield *et al* have noted a sustained rise in plasma antithrombin titer following in vivo trypsin administration They have postulated therefore that antithrombin activation may be an intravascular response to blood trypsin content

Welch and also Levy in discussing the report of Moseley *et al* felt that the antithrombin reaction was not specific for pancreatitis While the changes in blood clotting factors found in clinical and experimental pancreatitis resemble those seen after the intravenous administration of trypsin Grossman suggests that they may be due to other factors

b) *Alterations in Blood Chemistry* As already mentioned in connection with changes in prothrombin content of the blood those changes in chemical characteristics of the serum which reflect impaired liver or renal function are discussed together with other data concerning the function of these organs Furthermore changes in serum enzyme content in pancreatitis are also discussed separately Of the remaining biochemical substances in the serum probably the most profound alterations occur with respect to the concentration of electrolytes Thus Edmondson *et al* have found hypokalemia in 19 of 27 patients with acute pancreatitis Alkalosis intravenous saline administration nasogastric suction to relieve paralytic ileus and an increased production of ACTH have all been considered as playing a role in the production of such a low serum potassium On the other hand the break

was below 8 5 mg per cent in only twelve the lowest value recorded was 7 5 mg per cent and there were no cases with clinical manifestations of tetany

Certain possible relationships between diabetes and pancreatitis have been presented in Part I but in addition a number of investigators have noted transient hyperglycemia and glucosuria during attacks of acute pancreatitis (Zoepffel Archibald Stetten Bernhard Tammann DeTakats and Mackenzie Brocq and Varangot Brocq Robbins Henderson and King Love Walzel Elman Shumacker) In general the frequency has varied between 6 and 16 per cent Brocq and Varangot have attributed this to the destruction of insulin by trypsin but it may also result from impaired vascular function during an attack with temporary impairment of insulin delivery from the islets With resolution of the acute pancreatitis the hyperglycemia usually disappears Bernhard has stated that alterations in the glucose tolerance curve are more common than either hyperglycemia or glycosuria and this would tend to support impaired islet function

As previously mentioned an increase in plasma lipids mainly neutral fat but also cholesterol and phospholipids occur in some cases of recurrent pancreatitis Coffey and also Gardner and Fawcett have observed hyperlipemia in acute pancreatitis along with a milky serum which persists for weeks and may be related to a deficiency of a fat utilizing substance normally elaborated by the pancreas as previously discussed This lactescence of the serum may persist even during symptom free periods Albrink and Klatskin have recently reported that all lipid components but especially the neutral fat component are increased in alcoholic patients with a similar lactescence of serum

Wang *et al* have recently studied the effect on serum lipid levels of experimentally induced acute pancreatitis in dogs and rabbits The latter was accomplished by the instillation of staphylococcus toxin into the ligated pancreatic duct In rabbits cholesterol levels averaged 109 mg per cent phospholipids 286 mg per cent and total lipids 1142 mg per cent as compared with 50 105 and 350 mg per cent respectively in controls in which the pancreatic ducts were ligated and injected with normal saline

fat necrosis where saponification of the liberated fatty acids occur to form the corresponding calcium salts as previously noted It is pertinent in this regard that postmortem analyses have revealed an estimated 1700 2000 mg of calcium in the pancreas Another explanation of the low serum calcium is that excessive stimulation of the adrenals by ACTH may promote calcium excretion into the bowel Hayes has postulated that the ionized calcium is decreased due to the increased level of fatty acids in the serum associated with the elevation in serum lipase Since ionic calcium may be bound to fatty acids the tetany may not respond to calcium administration and parathyroid hormone may have to be administered to increase the ionic calcium If this explanation is a valid one it would also constitute a mechanism whereby intrinsic parathyroid stimulation would occur as discussed in connection with the association of hyperparathyroidism and acute pancreatitis

It would thus appear that when serum electrolyte changes occur in acute pancreatitis they usually consist of an increase in potassium and chloride and a decrease in magnesium sodium and especially calcium Carbon dioxide combining power is variable but usually normal alterations in such capacities if they occur are usually mild In only a few of our cases were determinations of all of these elements recorded Abnormal potassium determinations were recorded in only ten of the 17 cases with fulminating pancreatitis and these all showed serum elevations slightly above 5 mEq/liter Serum magnesium levels were not obtained in any of the cases in this series Sodium and chloride levels were recorded in about half of the 163 cases of acute pancreatitis but were usually within normal limits In five of the 17 cases in which acute pancreatitis was the major disease process low values for sodium and chloride were recorded with sodium serum levels ranging between 120 and 250 mg per cent and chloride between 220 and 300 mg per cent Carbon dioxide combining capacity was recorded in only 22 of the 163 cases and was also normal in most instances Four of the cases with fulminating pancreatitis showed CO capacities between 70 and 80 volumes per cent and two others between 30 and 40 Serum calcium determinations were carried out in 37 of the 163 cases and

Normal individuals maintain a normal diastase level and Roe *et al* have reviewed the literature and added experiments of their own showing that even after pancreatectomy the levels of amylase in the blood urine and tissues are not significantly altered they suggest that some organ or organs other than the pancreas may be the source of blood urinary and tissue amylase Certain older observations are also pertinent in this regard and have been reviewed by Gray *et al* The salivary glands and the pancreas of course contain large amounts of diastase but certain other body tissues and fluids do not contain this enzyme Hepatic bile normally contains no diastase except when the blood level is greatly increased and cerebrospinal fluid of normal persons likewise is free of this enzyme Liver kidneys and spleen contain diastase and it has also been found in lymph pericardial fluid feces skin muscle and human milk However it remains uncertain *whether the enzyme in many of these organs is contained* within the cells or in the intercellular fluid

Somogyi has shown that normally blood amylase does not originate either directly or indirectly in the salivary gland However the possibility appears not to have been excluded that a compensatory amylase synthesis may take place in other organs as a response to pancreatectomy Challis *et al* have recently shown that the administration of ACTH and the consequent activation of the adrenal cortex increases the mean serum amylase value about 40 per cent It is not certain from this observation whether the adrenal cortex secretes amylase or stimulates its secretion in some other organ possibly even the pancreas since *these dogs were not pancreatectomized* The role of adrenal corticoids in this regard deserves further study since there is a known increase in adrenal activity in acute pancreatitis On the other hand Polowe has observed an elevation in serum amylase in adrenal cortical insufficiency in the dog At any rate an increase in serum amylase value of 40 per cent is considerably smaller than that which usually occurs in acute pancreatitis

It is generally accepted that a sudden marked elevation in circulating amylase is a highly significant indication of acute pancreatitis A typical curve of alteration in serum amylase levels in this disease is shown in Figure 2 There is usually a rapid rise

Similarly in dogs the experimental group showed an average serum cholesterol of 295 mg per cent average phospholipids of 469 mg per cent and average total lipids of 1126 mg per cent as compared with 170 340 and 765 mg per cent respectively in controls

Low blood vitamin A and D levels commonly occur in chronic pancreatitis with steatorrhea This is attributed to an inability of absorption of fats and fat soluable vitamins in diseases of pan creatic insufficiency (Cantarow and Trumper)

e) *Alterations in Serum Enzymes* Probably the earliest work on serum enzyme changes in acute pancreatitis evolved around amylase because of the availability of methods for the quantitative determination of serum levels of this enzyme Thus the presence of diastase (amylase) in human blood was first noted by Magendie (1846) and Cohnheim (1863) found it in urine and traced the origin of urinary diastase to the blood Gray Prob stein and Heifetz have reviewed the early literature in this re gard They point out that the contradictory results of early inves tigations can to a large extent be attributed to inaccuracies of method With the development of the Somogyi technique at this hospital and its general adoption results have been more con sistent With this technique normal serum values range between 80 and 100 units this means that 1000 cc of blood plasma in cubated with starch for 30 minutes under standard conditions would produce reducing substances that would reduce as much copper as 80 180 mg of glucose Various modifications of meth ods for determining amylase (Fishman and Doubilet Peralta and Reinhold) have been evaluated by Machella Wohlgemuth (1909) appears to have been the first to detect an elevation in both blood and urinary amylase in acute pancreatitis and similar elevations have been observed in experimental pancreatitis produced by in jection into the ducts at low pressure various chemical substan ces bacterial suspensions and bile (Archibald Dragstedt *et al* Olsen *et al*) by ligation of the pancreatic duct (Clerc and Loe per Gould and Carlson Van der Erve King Kasahara and Ta kaishi Johnson and Wies McCaughan) and by induced trauma (Wohlgemuth and Noguchi DeTakats and Nathanson)

are on the descending part of the curve Furthermore there seems to be no constant relationship between the severity of the attack and the peak diastase level This consideration is well illustrated in the present series of cases In twelve of the cases serum amylase determinations were carried out in sufficient numbers and with enough frequency to plot curves all of these showed peak levels in excess of 1000 Somogyi units On the other hand there were 52 cases of acute pancreatitis in which only a single determination was recorded and of these only 16 (31 per cent) had recorded values in excess of 1000 units Eight of the latter were in the group of 17 cases of fulminating pancreatitis of the remaining nine single values of less than 300 were recorded in five instances and four showed values between 300 and 900 units

Gray *et al* have also pointed out that occasionally persistently elevated levels are obtained without obvious cause sometimes with renal disease (Bauman) in peptic ulcer perforating acutely into or near the pancreas (Mahner Foged MacDougall Bauman) and in peritonitis due to various causes (Raffensperger) With regard to the latter Rosenburg and Akgun have recently reported two cases of freely perforated ulcer one duodenal and the other gastric in which serum amylase levels of 812 and 1260 units respectively were found They point out that usually in such cases the serum amylase is only moderately elevated but that sometimes in situations in which pancreatic secretion has been stimulated by the intake of food or alcohol shortly prior to perforation the spillage of amylase into and rapid absorption from the peritoneal cavity may give a serum amylase value comparable to that found in acute pancreatitis as suggested by Mahaffey *et al* and by Pemberton *et al*

Since sedatives particularly morphine (Wapshaw) may produce spasm of the sphincter of Oddi and thus produce serum amylase elevations it is important that blood be drawn when patients are not under the influence of such drugs Moderate elevations in serum diastase usually not as high as in pancreatitis may also occur in disease of the salivary gland such as mumps suppurative parotitis and calculi obstructing salivary ducts (Bauman Spittuler) as well as after thyroidectomy (Gogol

to a peak 4 6 times the normal level followed by a descent Foged and also Elman have found that peak values may be attained as early as 24 36 hours after onset although this is variable and the return to normal occurs within three to four days in uncomplicated cases Sometimes the elevated amylase level may persist for long periods MacKenzie mentions a case in which it persisted for as long as twelve days and McCorkle and Goldman up to 22 days Such persistent elevations may indicate a continuation extension or progression of the process

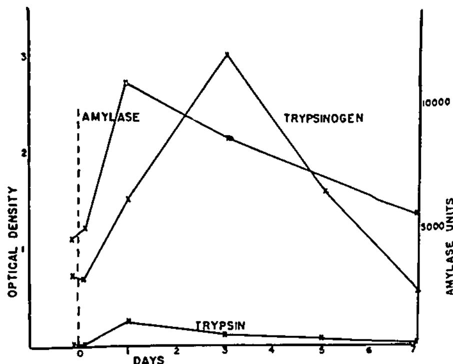


FIGURE 2 Serum enzyme levels in acute pancreatitis induced by pancreatic duct ligation followed by trypsin injection 24 hours later Dotted line indicates time of trypsin injection (From Powers S B Jr Brown H H and Stein A The pathogenesis of acute and chronic pancreatitis *Ann Surg* *142* 690 1955)

The time dependency relations in the typical curve may explain those cases of acute pancreatitis which fail to show elevated serum amylase levels since the timing of determinations may be such that peak values have passed and the values obtained

the disease in patients seen several days after onset Apparently some of these variations may relate to severity and others to recurrence still others may depend upon the amount of residual pancreas capable of producing amylase During the most severe attacks culminating in early death blood enzyme values may be markedly decreased due to destruction of the pancreas or to the formation of a large pseudocyst into which all of the enzymes are drained instead of passing into the blood stream

Elevations in serum lipase levels comparable to those for amylase also occur in acute pancreatitis The Cherry and Crandall method is the one in general use for the determination of serum lipase activity but it has the disadvantage of requiring 24 hours for completion Values above 1 0 ml of N/20 NaOH are considered significant by some observers (Raffensperger Cummins and Bockus Bockus and Raffensperger) and above 1 5 ml by others (Comfort Comfort and Osterberg) A more rapid method has recently been reported by Alper

The curve of lipase activity shows an initial rise similar to that for amylase and elevated values may persist 10-14 days or longer (Bockus and Raffensperger Comfort and Osterberg Richman) For this reason an accurate diagnosis of pancreatitis is often possible by means of lipase determinations after the serum amylase has fallen to normal levels In their series of 78 cases of acute pancreatitis Bockus *et al* have found that the serum lipase tended to be relatively lower than the amylase concentrations but the former did not show as much fluctuation as did the latter On the other hand Dreiling *et al* have been unable to find a consistent relationship between serum lipase levels and acute pancreatitis

Cantarow and Trumper state that unlike amylase increases in serum lipase occur in 40-50 per cent of cases of carcinoma of the pancreas 60 per cent of cases of carcinoma of the ampulla of Vater and 10-15 per cent of cases with chronic biliary tract disease similar elevations occur in intestinal obstruction (Raffensperger *et al* Johnson and Bockus Johnstone) duodenal ulcer cholelithiasis jaundice and hepatic tumors (Johnson and Bockus) hepatitis (Cummins and Bockus) and cirrhosis of the

Morris) In many of these instances however associated pancreatitis appears also to have been present or at least not excluded Serum amylase elevations have also been reported following operations in or outside the abdomen (Dunphy *et al* Hotchkiss *et al* Warren) and again pancreatitis has either been observed or not excluded MacKenzie has reported a case of small bowel obstruction with gangrene of the terminal ileum and elevated amylase levels and similar cases have also been observed by Polowe and by Raffensperger In such instances an accumulation of pancreatic secretion in the static intestinal content with subsequent absorption may also give high amylase values However as Heifetz has shown human succus entericus collected separately from both the isolated loops of jejunum and ileum and thus unmixed with secretions from other portions of the digestive tract contains no amylase nor is this absence of diastase affected by physiologic activities or by appreciable elevation in blood diastase

Further biliary tract disease unaccompanied by acute pancreatitis does not give an elevation in diastase levels On the contrary many cases of biliary tract disease when associated with impaired liver function present according to Somogyi subnormal diastase values Serum diastase levels are usually normal in chronic pancreatitis pancreatic cysts and in fibrosis and calcification of the pancreas but usually rise with acute exacerbations in recurrent pancreatitis and occasionally with carcinoma of the head of the pancreas producing obstruction of the pancreatic duct In the case of recurrent disease with progressive and extensive damage of acinar cells too few of the latter may remain to give an elevation during the acute flare ups

Finally, McCorkle and Goldman have reported six different curves of serum amylase activity in a group of 43 cases of acute pancreatitis (1) A sharp rise and fall to normal the typical curve as described above (2) A sharp rise and fall to subnormal levels (3) Fluctuations within the normal zone and slightly above and below the usual normal range (4) Sustained high values which may occur in extension or continuation of the disease, (5) Secondary elevations several days after fall to normal levels due to exacerbations and (6) Slight elevations late in

Powers *et al* have pointed out that there is a regular rise in serum trypsinogen following the onset of acute pancreatitis with necrosis comparable to that observed with amylase or lipase Trypsin appears in the circulation only when the quantity of this substance released exceeds the amount necessary to neutralize all of the antitrypsin It is therefore only in the more severe cases that active trypsin can be demonstrated In addition to the rise in trypsinogen and trypsin there is also a rise in plasmin and plasminogen which they consider non specific occurring also after many types of operative procedures For this reason a rise in total proteolytic activity at least in pancreatitis associated with surgical procedures may not be an accurate measurement One might anticipate an entrance of trypsinogen and chymotrypsinogen into the blood in acute pancreatitis but the presence of these proteases in blood has not been demonstrated As Grossman has pointed out blood plasma contains relatively potent inhibitors of these enzymes as well as other proteases not easily distinguishable from the pancreatic proteases notable among these is plasmin (Rush and Clifton)

On the other hand these alterations in components which play a role in blood coagulation afford indirect means for determining blood trypsin levels Loomis as well as Innerfield *et al* have shown that trypsin combines unimolecularly with antifibrinolysin in the blood and the circulating level of the latter which is a trypsin inhibitor falls Trypsin converts prothrombin to thrombin which it then destroys (Loomis Innerfield *et al*) and also lyses fibrinogen so that measurements of fibrinogen levels in the blood may also reflect levels of trypsin activity Elliott *et al* have injected graded doses of trypsin into dogs and measured their antifibrinolysin and fibrinogen levels They have compared these responses with the levels of antifibrinolysin and fibrinogen in experimental pancreatitis in dogs and in human cases with inflammatory disease of the pancreas They have concluded from these measurements and comparisons that considerably less trypsin appears systemically following pancreatitis than is well tolerated by the dog following the intravenous injection of this enzyme

liver (Cummins and Bockus Johnson and Bockus) peritonitis (Raffensperger) chronic pancreatitis and pancreatic ductal ob struction (Machella) As with serum amylase the administration of morphine sulfate (Bogoch *et al* Wapshaw) or codeine sul fate (Gross *et al*) may produce spasm of the sphincter of Oddi and elevation of serum lipase activity In addition Guszich has *found elevations in serum lipase levels in the postoperative* course of eleven of 16 patients following cholecystectomy and in seven of eight after gastrectomy *He ascribes these findings to* manipulation of the pancreas but cannot explain similar ele vations in 50 per cent of abdominal operations in which the pancreas was not touched Certain of these patients had appar ently been given sedatives which may account for some of the increases in serum lipase activity In general however it would appear that serum lipase levels are affected by many more fac tors not associated with pancreatic disease than are the levels of serum amylase activity

Undoubtedly alterations in serum trypsin levels also occur in acute pancreatitis but because of antitryptic factors in the blood which inactivate this enzyme the development of a satis factory method has been difficult Coffey *et al* have suggested that the measurement of the antitryptic activity of the blood might be useful in differentiating acute necrotizing from acute edematous pancreatitis Powers *et al* have found that when serum is subjected to a temperature of 60°C plasminogen plasmin and the antitryptic factors are inactivated while trypsin and trypsinogen remain stable and can then be measured In this procedure the serum is divided into two parts one of which is di *rectly tested for its proteolytic activity on casein and the second* activated with enterokinase prior to the exposure of casein The *first* then gives a measurement of immediate proteolytic activity presumably due to the presence of trypsin while the second includes active trypsin plus activated trypsinogen the difference between the two represents the amount of proteolytic enzyme originally present as trypsinogen Recently Nardi and Lees have reported a method for determining serum enzyme levels utilizing synthetic C benzoyl 1 arginine amide hydrochloride

The occurrence of necrosis of pancreatic parenchyma introduces an additional factor in that this process releases enzymes into the interstitial spaces from which they are absorbed into the blood stream As each acinar cell disintegrates in the necrotizing process its total enzyme content becomes available for such absorption and this process continues until cell death has ceased The attainment of a peak serum enzyme level then simply represents the phase at which absorption of enzymes into the blood is greatest in relation to the rate of excretion in the urine In the case of transient obstruction of the pancreatic duct without accompanying acinar necrosis the attainment of a lower but more prolonged maximum may occur because a state of equilibrium may exist between the rate of enzyme release into the blood stream from cells which continue to produce enzymes and the rate of urinary excretion A descent from this maximum may then indicate either a release of the pancreatic ductal obstruction or a cessation of secretion of enzymes by the acinar cells possibly due to exhaustion That these processes may vary in intensity is indicated by the lack of agreement as to when a maximum serum enzyme level is attained Thus Warren states that a peak level for amylase is to be expected within 48 to 72 hours after the onset of an attack while Lewison reports peak levels within the first 48 hours and Wapshaw between the fourth and sixth hours The subsequent rate of decline is also variable it may be rapid (Heifetz *et al* McCorkle and Goldman) or remain elevated for many days (Heifetz *et al*) Lewison believes that the duration of elevation may have prognostic value

Another route of entry of enzymes into the blood has been suggested by Naffziger and McCorkle who have observed that in cases of pancreatitis due to trauma serum amylase elevations may be due to peritoneal absorption of enzyme Some correlation between serum enzyme level and that of the peritoneal exudate has also been reported by Popper and by Walzel Ivy and Gibbs have also shown that amylase in peritoneal exudate contributes appreciably to the serum level but Howard *et al* believe this is not as large as that which is absorbed directly into the pancreatic venous blood The characteristics of the peritoneal fluid may furnish information as to the type of pancrea

Obviously the mechanism whereby these enzymes gain entrance into the blood relate to phenomena occurring in the pancreas Popper and Necheles have shown that when the pancreatic duct is ligated and bile introduced into it, the increase in blood amylase and lipase is due mainly to the inflow of pancreatic enzymes into the general circulation by way of the portal vein through the hepatic venous circulation and only to a smaller extent to the inflow of enzymes by the lymph of the thoracic duct Howard *et al* have also demonstrated markedly increased enzyme levels in the pancreatic veins following trauma to the pancreas *In both of these studies however injury to pancreatic* tissues with necrosis was present so that there was more than simple ductal obstruction

On the other hand Tuchman *et al* have observed a considerable rise in serum amylase of normal dogs four hours after the injection of mecholyl while only a minimal response was obtained in pancreatectomized dogs the concentration in the pancreatic arteries was not elevated Antopol *et al* have demonstrated *the ability of acetylcholine also to produce an increase* in blood amylase titer of normal dogs and of physostigmine to increase markedly the blood amylase response to acetylcholine On the other hand atropine inhibits the response to acetylcholine Such observations indicate that simple ductal obstruction without significant injury to acinar tissue can also cause a rise in serum enzyme levels a conclusion supported by the study of Byrd and Sawyer who found that transient obstruction of the pancreatic duct in the dog for as short a period as two hours produced elevation in serum amylase 1 7 to 3 times the preoperative value Such observations along with others previously mentioned indicate that a rise in intraductal pressure from whatever cause may accelerate the passage of enzymes into the venous *blood It seems* likely that when the intraductal pressure exceeds a critical value perhaps that of the interstitial tissue or of the pressure of the pancreatic venules there is a reversal of dominant direction of secretion by the acinar cells from the ductal side to the surface facing these small vessels Such pressure considerations would also account for the absence of elevated amylase levels in the arterial circulation

may be transitory or they may be persistent Thus transitory hyperlipemia (Gardner and Fawcett) transitory ketonuria (Machella) transitory retention of sulfobromophthalein (Bockus *et al*) and transient hypoprothrombinemia (Bockus *et al*) have been observed in association with acute pancreatitis Such a temporary derangement of these values indicating impaired liver function have in general been correlated with the duration of an acute attack of pancreatitis and thus in all likelihood reflect an effect of the pancreatic disease on hepatic function

Hyperlipemia and hypothrombinemia of a more persistent character have been discussed in previous sections and may reflect alterations which occur within the pancreas itself

It appears to be the general experience that a persistent hyperbilirubinemia occurs in some patients with acute and chronic pancreatitis Thus Bockus *et al* found the bilirubin levels more markedly elevated in patients with biliary tract disease and pancreatitis than in those with alcoholism and pancreatic disease In both groups the hepatic disease probably preceded the pancreatitis and may have been causally related Richman has found an elevation in serum alkaline phosphatase levels in 10 3 per cent of patients with acute pancreatitis and Bockus *et al* in 11 6 per cent In most instances here too it is likely that these elevations reflect biliary tract disease which was causally related to the pancreatitis On the other hand Grossman *et al* believe that while an elevation of serum alkaline phosphatase may reflect biliary obstruction a block in the pancreatic ductal system may also cause an increase of pancreatic alkaline phosphatase

In the study of Healey *et al* in the majority of cases in which acute pancreatitis was the principal cause of death the total serum protein as well as albumin and globulin components was below normal this was also true of the postoperative group However in the group in which the pancreatitis was only an associated and not the major disease process one half of the cases showed a low total protein and 75 per cent low albumin values while 75 per cent showed an increase in serum globulin These observations suggest that in acute fulminating pancreatitis

titis a yellow turbid fluid indicating edematous type while a reddish brown fluid may indicate hemorrhagic type The presence of bile and hydrochloric acid may indicate the presence of a perforated peptic ulcer Keith *et al* and Zollinger *et al* have also measured the amylase activity in paracentesis fluid of patients with acute pancreatitis the concentration of enzyme is increased to 300 or more Somogyi units and may remain so for 2 4 days after the blood level has returned to normal

An increase in serum amylase activity is apparently without harmful effects Likewise an elevation in serum lipase levels per se also appears harmless and even its effects on fatty tissues into which it may diffuse are without systemic reaction because of the precipitation of insoluble calcium soaps Moderate amounts of pancreatic proteases in the blood also may be tolerated and indeed trypsin has even been advised for therapeutic purposes (Innerfield *et al*) However larger amounts produce profound shock and death (Rocha *et al*) Others have attempted to attribute the shock and death of severe acute pancreatitis to circulating proteases (Rush and Clifton Hoffman *et al* Shinowara *et al*) However attempts to counteract this effect by the use of purified soybean trypsin inhibitor have yielded equivocal results (Rush and Clifton Hoffman *et al*)

d) *Hepatic Function* The problem of evaluating the significance of liver function with pancreatitis is a complicated one As discussed in Part I in some situations liver disease appears to play a causal role either directly or indirectly while in others it may for one reason or another be the result of acute pancreatitis It is frequently impossible to distinguish between these two possibilities clinically although the duration of hepatic disease may offer an important clue

Investigators concerned with hepatic function in acute pancreatitis have employed a battery of tests to demonstrate associated liver disease among the more frequently utilized ones are the cephalin cholesterol flocculation thymol turbidity sulfobromophthalein retention serum bilirubin level serum lipid levels albumin globulin ratio serum alkaline phosphatase activity and prothrombin concentration Abnormal results with such tests

acute pancreatitis have been mentioned in Part I These may be manifested biochemically by transient albuminuria which according to Richman is present in about 25 per cent of cases of acute pancreatitis or by marked suppression of urine in those cases which develop a lower nephron syndrome (Renner) The latter is probably due to a diminution of the effective glomerular filtration pressure incident to shock The high incidence of nitrogen retention in association with acute pancreatitis has also been presented in Part I Taylor has listed the frequency of various abnormal urinary findings in a series of 110 cases of acute pancreatitis as follows

Albuminuria	24 5 per cent
Increased diastase	13 6 per cent
Glycosuria	12 7 per cent
Bile positive	10 8 per cent
Dysuria	6 3 per cent
Acetonuria	5 4 per cent
Hematuria	3 6 per cent
Oliguria	0 9 per cent

In our series of 163 cases albuminuria was present in 15 3 per cent glycosuria in non diabetics in 5 per cent bile positive urine in 9 8 per cent hematuria in 23 3 per cent and oliguria in 2 4 per cent Except for glycosuria oliguria and bile in the urine these data as well as the corresponding data of Taylor may be misleading since many of these patients undoubtedly had chronic renal disease unrelated to pancreatitis Urinary diastase levels were recorded in 21 of our cases (13 per cent) and were elevated above 1200 Somogyi units per hour in 19 (90 per cent)

As pointed out in a preceding section the level of serum enzymes at any given moment is in part dependent upon the rate of excretion in the urine According to Nothmann the normal urinary level for amylase as determined by the Somogyi method ranges from 80 to 300 units per 100 ml Others have measured urinary content for amylase in terms of units per hour and Dankner and Heifetz state that it is about 1200 in normal persons Gray and Somogyi have reported a parallelism between the blood and urinary diastase curves In acute pancreatitis the urine values usually rise shortly after those in the blood and elevated urinary levels may persist for from one to three days and then fall sharply to normal

there is insufficient time for the compensatory phenomenon of an elevation of serum globulin to occur

With the remaining tests listed above Bockus *et al* have found that 20 per cent of the alcoholic group and only 4 per cent of the biliary tract group with acute pancreatitis had evidence of impaired liver function On the other hand on the basis of the same battery of tests Howard believes that hepatocellular damage occurs rather frequently with acute pancreatitis and parallels the degree of pancreatic damage He suggests that the impaired liver function may be due to common bile duct obstruction although such patients are not as a rule jaundiced or to a bacterial or enzymatic cholangitis Evidence for common bile duct and pancreatic duct obstruction as a result of compression by the edematous head of the pancreas has been discussed in Part I and may possibly account for associated impaired hepatic function

A battery of hepatic function tests comparable to that utilized in the preceding studies was carried out in 60 of the 163 cases (37 per cent) in the present series The frequency of evidence of impaired liver function is tabulated below and related to etiologic groups as presented in Part I As would be expected the highest percentage was found in the group with obstructive disease of the biliary or pancreatic ducts Intermediate frequencies were found in the infectious and metabolic groups and lower frequencies in the vascular and idiopathic groups in which acute pancreatitis was *frequently only an incidental finding* at autopsy In general these data appear to simply reflect the frequency with which clinical symptoms raised a suspicion of hepatic disease which was corroborated by laboratory studies

Etiologic Group	*Number of Cases with Tests for Hepatic Function*	*Number of Cases with Tests Showing Impaired Hepatic Function*	*Per Cent*
Obstructive	20	15	75
Infectious	10	5	50
Metabolic	12	5	42
Vascular	6	2	33
Idiopathic	10	2	20
Traumatic	2	0	0
Allergic	0		

e) *Renal Function* Renal lesions found in assoc[illegible]

These are mentioned here because of the influence of impaired renal function on the excretion of amylase and because Dozzi has stated that the urinary diastase values are less reliable when marked glycosuria is present The data on blood and urinary diastase are tabulated below the groupings were made on the basis of blood diastase levels and were so arranged as to give approximately equal numbers in each group with the exception of the one in the 200 400 unit range where there were 23 cases From the blood diastase ranges if 400 is taken as the dividing line it is apparent that in about twenty of these cases determinations were made during an attack of acute pancreatitis while the remaining 29 were probably not suffering from this disease The data show further that while there is great individual variation in urinary diastase values in any particular group there is in general an increase in average urinary diastase output as the average blood level for this enzyme increases Furthermore the ratios determined on the basis of the average urinary and blood levels in each group rather than on the basis of the ratio in each individual case show a fairly narrow range of variation (1 7 3 3) It would thus appear that as a generalization there is a correspondence between urinary and blood diastase levels although this may be upset by a number of factors particularly impairment of renal function Gray and Somogyi have reported that the Urine/Blood ratio under normal conditions and under conditions resulting in an increase in blood amylase is greater than unity and our tabulation substantiates this conclusion On the other hand a reversal of this ratio was observed by Gray and Somogyi in a variety of kidney disturbances and a ratio of less than unity may therefore indicate severe renal disease

Number of Cases	*Blood Diastase Range*	*Average Urinary Diastase Levels*	*Ratio*
6	100 200	343 7 (126-570)	2 5
23	201-400	672 3 (85 1368)	2 5
7	401-800	2282 6 (86-5803)	3 3
7	1000-3000	2869 1 (950-4886)	1 7
6	3000 10 000	1 1646 3 (955 2 3750)	2 0
49			

Determined as Somogyi units
Determined as Somogyi units per hour
Figures in parenthesis represent range of variation

Some investigators believe that determinations of urinary levels to be less reliable than blood (Lewison Popper and Necheles Faergemann and Rasch Dozzi von Benczur) and Dozzi has concluded from experiments in dogs that there is no quantitative relationship between the blood and urine diastase On the other hand Dankner and Heifetz have found that in the human there is a close relation between the blood diastase levels *and the rate of urinary excretion throughout the course of* an attack of acute pancreatitis although there is some variability in the urine/blood ratio at each time period in the curve The time which elapses before the elevation of blood diastase results in an increased urinary excretion of this enzyme is less than two hours and probably a matter of minutes providing renal function is normal However they found that during an attack of acute pancreatitis impairment of renal function commonly occurs even in the absence of clinical shock as shown by concomitant determination of blood and urinary creatinine levels Such renal impairment is usually greatest 24 48 hours after the onset of an attack generally lasts 12 36 hours and retards the descent of blood diastase levels

When renal function is impaired very early in the course of acute pancreatitis the initial elevation of urinary diastase may also be retarded Failure to recognize such abnormalities in renal function may explain the impression of some investigators (Gray *et al* von Benczur Paxton and Payne) *that many hours are re*quired for elevated blood diastase to result in elevated urinary diastase Saxon *et al* have recently studied concomitantly obtained specimens of urine and blood from patients with acute pancreatitis utilizing a two hour urine specimen They found the determination of urinary amylase excretion a more sensitive indicator of pancreatic disease than that of the blood level in patients with adequate urinary function

Dr Somogyi has kindly made available to us data on 49 patients consisting of concomitant blood and urinary diastase determinations as well as blood sugar and NPN Only four of these patients showed NPN values in excess of 50 mg per cent and only seven patients had blood sugar values in excess of 100 mg per cent with the highest recorded as 162 mg per cent

gested that a low serum postassium concentration may be responsible while Bauerlein and Stobbe believe that fat necrosis in the myocardium or some remote biochemical effect of such fat necrosis is responsible Doublet and Mulholland have suggested an action of trypsin on the myocardium

Siler and Wulsin have been unable to demonstrate a consistent electrocardiographic pattern in acute pancreatitis but advance two additional suggestions as to possible mechanisms involved (1) a low serum calcium level and (2) a disturbance of the vagal impulses via the celiac plexus

g) *Respiratory Function* Howard has emphasized the high incidence of pulmonary atelectasis in acute pancreatitis which he believes is secondary to a paralytic ileus and abdominal distention In addition the association of pleural effusion which Howard has attributed to subdiaphragmatic inflammation has been discussed in Part I Case has also emphasized the frequency of pleural exudation on the left side Poppel has called attention to the socalled Fleishner lines on x ray of the chest which denote linear focal atelectasis Particularly interesting is the observation of Coffey that when pleural effusion occurs as a complication of acute pancreatitis the aspirated thoracentesis fluid may contain significant amounts of amylase

h) *Gallbladder Function* The voluminous literature on the relationship between gallbladder disease and acute pancreatitis has been presented in Part I mainly from the standpoint of the causal role of such gallbladder disease On the other hand Kaden *et al* as well as Sylvani and McCorkle have presented evidence of impaired function of the normal" gallbladder during acute pancreatitis In the latter study intravenous cholecystography revealed a failure of gallbladder visualization in 16 of 28 patients with acute pancreatitis which persisted for a week after which the gallbladder regained the function of dye concentration While unable to explain this phenomena Sylvani and McCorkle could find no evidence of an inability of the liver to excrete dye Radakovitch *et al* have suggested that obstruction of the pancreatic duct may prevent absorption of the cholecystographic media and Kaden *et al* have presented the idea that concomitant paralytic

Cantarow and Trumper have stated that elevated urinary amylase values may also be found in chronic pancreatitis when there are acute exacerbations in choledocholithiasis obstruction of the pancreatic duct and occasionally in carcinoma of the pancreas As in blood the levels do not necessarily reflect the severity of the disease

Machella and Richman both point out that urinary lipase studies have not been widely used and a satisfactory method for determining urinary trypsin is not available Scriba has reported the frequent occurrence of fat droplets in the urine following traumatic fat embolism and Scuderi reported the same finding following the intravenous injection of fat In light of Lynch's observations concerning fat emboli in the kidney in acute pancreatitis the demonstration of urinary fat might be expected However Klatskin and Gordon were unable to demonstrate fat in the urine in their study of relapsing pancreatitis and essential hyperlipemia

Cantarow and Trumper have stated that melanuria also occurs in rare instances in acute pancreatitis perhaps through some derangement in tyrosine metabolism in the pancreas

f) *Cardiac Function* Gottesman *et al* (1943) described transient changes in the electrocardiograms of five patients with acute pancreatitis simulating those of coronary occlusion As the patients improved following their attacks of acute pancreatitis these electrocardiographic changes disappeared There was a depression of the S T segment in leads II and III and a diaphasic T wave in leads I II and III One patient however succumbed and at autopsy a reddish brown fluid was found in the pericardium but there was no evidence of coronary occlusion or myocardial infarction These workers also produced rather marked electrocardiographic changes in experimental hemorrhagic pancreatitis in dogs Electrocardiographic changes have also been reported by other observers (Dittler and McGavack Bockus *et al* Bauerlein and Stobbe) and in several of these reports coronary occlusions were suspected clinically and not found at autopsy Richman believes that this may be due to coronary insufficiency secondary to shock On the other hand Bockus *et al* have sug

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ileus may prevent dye absorption Richman believes that edema and spasm of the biliary sphincteric mechanisms may prevent filling of the gallbladder The previously mentioned distortion and obstruction of the biliary pancreatic ductal systems by compression from the enlarged edematous head of the pancreas might act in a similar fashion

i) ***Gastrointestinal Function*** Distention or spasm of various segments of the gastrointestinal tract have been observed by a number of observers in cases of acute pancreatitis Howard has emphasized the occurrence of persistent paralytic ileus which may simulate obstruction of the left colon Case has demonstrated both distention of the colon and paralytic ileus by x ray and Richman has described an elevation of the stomach with enlargement of the duodenal loop as well as a defect in the region of the duodenal jejunal flexure Metheny *et al* have reported the presence of a gas bubble in the atonic duodenal bulb and Glenn and Baylin spasm of the duodenal loop with change in contour Spasm of various areas of the colon have also been observed by Glenn and Baylin Grollman *et al* have reported the occurrence of an isolated loop of distended small intestine similar to the sentinal loop in acute appendicitis and acute cholecystitis

Howard has attributed the paralytic ileus to retroperitoneal inflammation and to enzymatic chemical and bacterial peritonitis Glenn and Baylin believe that foci of fat necrosis may account for focal spasm of the colon

In the foregoing discussion it has been shown that the etiologic factors presented in Part I act essentially as mechanisms which upset a rather delicate balance between protective and autocatalytic factors normally resident in the pancreas thus permitting the latter to produce acute pancreatitis Certain components of these reactions in the pancreas are comparable to those which may occur in any organ but others are peculiar to the pancreas because of the catalytic substances which are present Likewise certain of the systemic reactions are comparable to acute inflammation occurring in any site in the body while others are characteristic of acute pancreatitis again because of the release of ferments into the circulation The effects on distant or

gans as demonstrated here, are considerably more frequent and widespread than appears to be generally appreciated

SUMMARY

Part I has dealt for the most part with those events which may set up a series of reactions in the pancreas leading to pancreatitis In this second part we have dealt primarily with those events which take place within the pancreas in the evolution of the disease process and with some of the secondary phenomena produced by the intrapancreatic disease The thesis has been propounded that in the pancreas there are potentially destructive forces as well as protective agents and that under normal circumstances these are in balance The etiologic processes described in Part I act to upset this balance either by activating the destructive forces or by reducing the effectiveness of the protective agents The destructive forces consist of the various digestive enzymes normally synthesized in the pancreas some of which require activation before they become destructive The mode of activation thus becomes important in understanding the initiation of acute pancreatitis Most students of the latter disease have attributed the destructive effects to trypsin and chymotrypsin but it is evident from the foregoing discussion that many other pancreatic enzymes play a role Some of the latter require no activation they become destructive when a mechanism is present which permits their movement into the interstitial tissues The actions of these many enzymes can account for the parenchymatous necrosis fat necrosis and hemorrhage the three major components upon which the pathologic physiology of the disease rests

The complications and sequelae of pancreatitis from the standpoint of pathologic physiology depend in part on the dissemination of enzymes and the products of their digestion by the lymphatic and blood circulation In part they are also dependent upon healing processes within the pancreas which may lead to scar formation and impairment of pancreatic function as dealt with in Part III Such scar formation may not only lead to a loss of parenchymatous tissue of the pancreas but also to impairment of the circulation and ductal structures and with the latter a

blockade of the movement of pancreatic secretion into the duodenum

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PART III

PATHOLOGIC ANATOMY

THE PATHOLOGY OF PANCREATITIS

In the preceding parts certain considerations regarding the anatomy of the pancreas which may play a role in the pathogenesis of pancreatitis have been discussed The presence for example of an anatomic arrangement of the pancreatic and biliary ductal systems which permit the reflux of bile into the pancreas is dependent in the first instance upon the course of embryologic development The route of spread of inflammatory products from the pancreas is determined by anatomic relations between the pancreas and adjacent organs as well as considerations of blood and lymph vascular arrangement Blood vascular arrangement is also important with regard to the potential for the development of collateral circulation in the event of vascular occlusion since it has been pointed out that the latter may play an important role in the pathogenesis of pancreatitis Furthermore there is a nervous regulation of pancreatic secretion and nerve supply is also important in an understanding of the distribution of pain and the occurrence of other symptoms which have been dealt with in Part IV Finally an appreciation of certain of the gross and microscopic characteristics of pancreatitis and its sequelae is dependent upon an understanding of the normal structural characteristics of the pancreas

In this part we have therefore dealt first with the normal embryology and anatomy of the pancreas then with the pathologic alterations which occur in this organ in pancreatitis and finally with the pathology of complications and sequelae

sung is derived from the duct of the dorsal pancreas. The normal lobulated appearance of the pancreas results from the ingrowth of surrounding mesenchymal connective tissue.

Because the duodenal end of the duct of Santorini remains small while the duct of Wirsung enlarges, the former becomes functionally a tributary of the latter, although it retains its duodenal outlet as well. The more common variations in the arrangements of these two ducts have been shown in Figure 1 and the frequency of each as found by various investigators appears in Table 7. Wapshaw has observed that in pigs, sheep, oxen and ruminants in general, the duct of Santorini usually serves as the main duct, and this has physiologic significance in that the principal bile salt, sodium taurocholate, in these species has a more drastic action on pancreatic tissue than sodium glycocholate, the principal bile salt in human bile; this ductal arrangement is therefore a protective one in that it does not permit the reflux of bile into the pancreas.

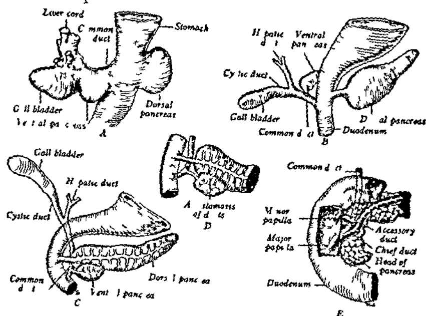


Figure 3. Development of the human pancreas shown by models viewed from the left side. A, at 6 mm (× 83). B, C, D, at 8, 12 and 16 mm respectively (× 42). E, at birth (× 1). (From Arey, L. B.: Developmental Anatomy, Sixth Edition. W. B. Saunders Co., Philadelphia, 1954, p. 257.)

Chapter 13

NORMAL EMBRYOLOGY AND ANATOMY OF THE PANCREAS

a) *Embryologic Development* As Arey points out two out pocketings of the entodermal lining of the gut represent the earliest indications of the future pancreas and these arise on opposite sides of the duodenum in the 3 4 mm stage One pushes out from the dorsal wall and becomes the dorsal pancreas and the other probably originally bilobular appears ventrally and consequently is designated as the ventral pancreas The dorsal pancreas grows more rapidly and by the sixth week is an elongate structure with a centrally coursing duct It extends into the dorsal mesentery and continues its growth within the dorsal layer of the developing omental bursa The ventral bud remains smaller and its duct is promptly carried away from the duodenum by the lengthening common bile duct and then arises directly from the latter The ventral pancreas together with the common bile duct then rotates around the duodenum to the right and posteriorly In its final position to the left of the duodenum and just below the duodenal primordium the ventral pancreas fuses along its distal border with the mid portion of the dorsal pancreas According to Arey the two primordia interlock intimately during the seventh week and no histologic distinction exists between the derivatives of the two components The fusion progresses towards the duodenum involving coincidentally a fusion of the ducts of the two primordia

The duct of the dorsal pancreas (duct of Santorini) may become constricted or even stenosed and in any event it remains in most individuals as the smaller or accessory pancreatic duct *The duct of Wirsung* the chief pancreatic duct is in its proximal third derived from the duct of the ventral pancreas and in most individuals empties together with the common bile duct into the duodenum at the papilla of Vater The dorsal pancreas forms all of the adult gland except the head which comes mostly from the ventral primordium The distal two-thirds of the duct of Wir

The head is a rounded but irregular disc lying closely against the first second and third parts of the duodenum The shape of the head varies usually with the form of the encircling duodenum and its diameter from above downward is rarely less than 7 cm Its separation from the neck is indicated by a groove on the front of the gland which contains the gastroduodenal branch of the hepatic artery The head rests posteriorly on the inferior vena cava sometimes on the right renal vein and lies close to the right suprarenal gland It lies at the level of the first and second lumbar vertebrae and often part of the third

The body including neck and tail has a triangular shape Because of its tortuous course it appears shorter than it really is Starting to the right of the spine at the level of the first lumbar vertebra it crosses the spine transversely to the left and extends as far as the spleen The tail may continue across the spleen and it usually turns downward towards the pelvis The neck is about 2 3 cm in length crosses the portal vein and is deeply grooved on its dorsal surface by that vein

An indication of the relationship of the pancreas to adjacent structures can be gained from its surface anatomy The *postero superior surface* is deeply grooved by the portal vein which may be entirely surrounded by pancreas To the left of the portal vein this surface faces first the inferior vena cava then the segment of aorta which lies between the celiac axis above and the superior mesenteric artery below The next portion lies consecutively on the left pillar of the diaphragm the left adrenal and the left kidney If the tail is long it may rest on the gastric surface of the spleen The splenic artery and vein lie in horizontal grooves on the posterior surface the lower one containing the vein being longer and deeper The venous groove extends from the tail of the pancreas to the portal vein while the one containing the artery extends from the origin of the latter at the celiac axis to the tail of the pancreas The *antero superior surface* is the largest it slants downward and forward forming a concavity which constitutes part of the stomach bed On the lower margin of this surface opposite the aorta there is a swelling the omental tuberosity this lies behind the lesser curvature of the stomach at the lower end of the vertical part of this curvature The inferior

The primordia are initially simple tubes of entoderm which branch extensively so that by the time fusion occurs there is an intricate duct system The acini begin to appear in the third month as terminal and side buds from the ducts The islets of Langerhans also differentiate from the ducts at about the same time The acini or zymogenic parenchyma constitutes the exocrine portion of the pancreas while the islets constitute the endocrine portion The latter are composed of distinctive cells which initially take the form of single sprouts, but later through growth and possible concrescence become complex island masses

Clark estimates that in all about a million islets are formed some of which retain their original connections with the parent ducts Although acini and islets originate from the same source they take different lines of specialization and once formed do not normally reconvert The various stages in the embryonic development of the pancreas are shown in Figure 3

Arey states that accessory pancreases are common Many of these lie within the wall of the intestine and stomach while others are associated with the spleen and omentum The development of the supernumerary primordia and the displacement of parts of the diffuse early pancreas are responsible for this distribution An annular pancreas encircling the intestine bile duct or portal vein also occasionally occurs These sites are mentioned because acute pancreatitis in ectopic gastric pancreas and in pancreatic tissue in a Meckel s diverticulum has been mentioned and this disease has also been found in annular pancreases

b) *Gross Anatomy of the Pancreas* The pancreas lies molded across the spinal column with its head on the right enclosed in the loop of duodenum and its tail on the left in contact with the spleen It is usually a light straw color although in a congested state it may appear red In the adult its weight usually varies between 65 and 160 gm and its specific gravity is about 1 045 The length in situ measures from 20 to 25 cm It consists of an enlarged descending part on the right the head and a long transverse body extending to the left towards the spleen the latter is usually divided into neck body and tail for descriptive purposes

surface is the smallest and rests on the lower layer of the transverse mesocolon It is rounded and irregular except for a smooth concave portion above the duodeno jejunal junction To the right of the ligament of Treitz it is grooved by the superior mesenteric artery Both inferior borders of the pancreas are notched by the superior mesenteric artery and the superior border by the celiac axis as well Certain of these relations are shown in Figure 4

As Siler and Wulsin have pointed out the word pancreas is derived from the Greek words pan meaning all and kreas which means flesh The literal translation all flesh indicates that the organ has a uniform composition and consistency and has no bone or cartilage Although there is considerable variability primary lobules as such rarely exceed 2 5 mm and the majority are 1 mm or less (Edmondson *et al*) It has no well defined capsule but is surrounded by a thin fibrous sheath which is continuous with the interlobular connective tissue Groups of lobules form secondary lobules measuring up to 5 6 cm in diameter The duct of Wirsung begins in the tail and courses through the center of the body toward the right when it reaches the head it turns downward and then to the right as it approaches the duodenum The branches which originate from this duct generally come off at right angles The duct descends to the wall of the duodenum ventral to the common duct and here it usually attains a diameter of about 5 mm The duct of Wirsung and the common duct usually enter the duodenal wall separately but they frequently join in the ampulla of Vater where their secretions mingle before discharge into the duodenum

The duct of Santorini maintains a vestigial but in some instances a functional outlet into the duodenum located at a point about 3 cm above and ventral to the papilla of Vater The left end of this duct joins the duct of Wirsung at the point where the latter curves downward into the head of the pancreas Since the duct of Santorini ordinarily decreases in size as it approaches the duodenum most of the flow of pancreatic juice into this duct is directed through the duct of Wirsung to the duodenum However as Siler and Wulsin have observed there are three circumstances under which the normal direction of flow may be changed (1) If no communication exists between the duct of

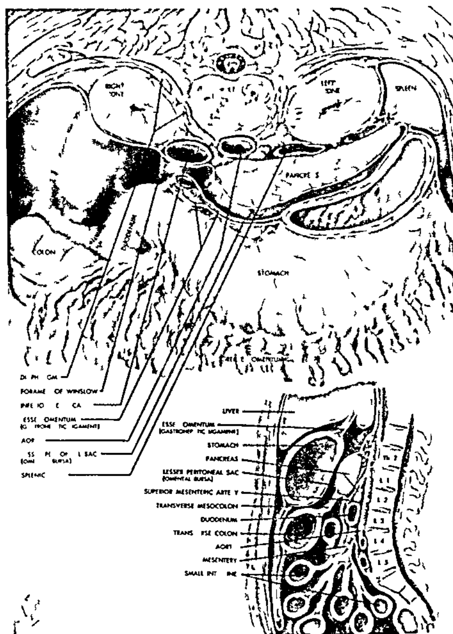


FIGURE 4 The Pancreas in Relation to Other Abdominal Viscera (Drawn by Netter F From Clifton E E Diseases of the Pancreas *Clinical Symposia* Ciba Pharmaceutical Products Co Vol 9 No 2 Summit N J 1957)

the major portion of the pancreas thus lies at the base of the lesser peritoneal cavity

c) **Blood Supply of the Pancreas** Olsen and Woodbourne have recently carried out a thorough study of the arterial supply to the pancreas and emphasize the fact that "the blood vessels around the pancreas are large important and more numerous than the current brief textbook accounts indicate" There are eight major arteries of the pancreas (1 2) anterior superior and posterior superior pancreaticoduodenal arteries (3-4) anterior inferior and posterior inferior pancreaticoduodenal arteries (5)

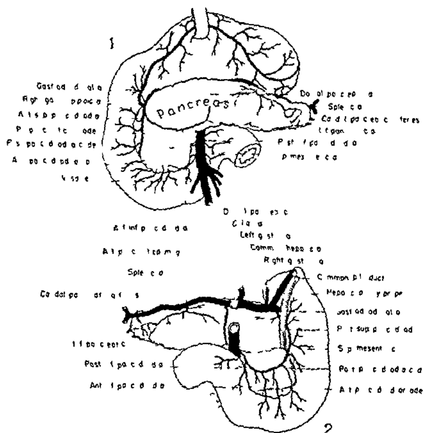


FIGURE 5 Vascular Relations of the Pancreas 1 Anterior View 2 Posterior View (From Olsen L L and Woodbourne R T The vascular relations of the pancreas Surg Gynec & Obst 99 713 1954)

Santorini and the duct of Wirsung (2) if the duodenal portion of the duct of Wirsung is congenitally stenosed or atrophic or (3) if the outlet of the duct of Wirsung is artificially obstructed

Cross has recently studied the distribution of the pancreatic biliary ductal system in over 400 autopsy specimens by various injection techniques He has pointed out that the descriptions in English language textbooks of anatomy histology and pathology give the impression that the common duct is a simple straight clean bore tube which joins the pancreatic duct passes through a sphincter and empties at the ampulla into the duodenum He shows that this is a great oversimplification and demonstrates the anatomical complexity of the intrapancreatic portion of the common bile duct and its continued functional relationship to the pancreas In most specimens the common duct in its intrapancreatic and intraduodenal portions is joined by many small ducts of pancreatic origin Many small pancreatic ducts also enter the lumen of the bowel directly particularly at the ampulla and in the second portion of the duodenum He has suggested that the term accessory pancreatic ducts should be extended to include the small ducts which join the intrapancreatic portion of the common bile duct and those which enter the lumen of the bowel directly

The position of the pancreas with regard to the peritoneum is important in determining the local spread of inflammation The embryonic ventral pancreas is suspended in the ventral mesentery of the primitive gut while the dorsal pancreas lies free in the dorsal mesentery The embryologic rotation of the duodenum to the right places the dorsal pancreas against the posterior abdominal wall where it loses its mesentery and becomes a retroperitoneal organ It thus becomes bound posteriorly to the retroperitoneal tissues and its posterior surface is thus not covered with peritoneum except at the tip of the tail Thus the pancreas lies at the base of the transverse mesocolon between the leaves of peritoneum which cover its antero-superior and inferior surfaces It lies between the greater and lesser peritoneal cavities at their separation by the transverse mesocolon in such a position that its broad antero superior surface faces the lesser cavity while the narrow inferior surface presents towards the greater cavity

the major portion of the pancreas thus lies at the base of the lesser peritoneal cavity

c) **Blood Supply of the Pancreas** Olsen and Woodbourne have recently carried out a thorough study of the arterial supply to the pancreas and emphasize the fact that the blood vessels around the pancreas are large important and more numerous than the current brief textbook accounts indicate There are eight major arteries of the pancreas (1 2) anterior superior and posterior superior pancreaticoduodenal arteries* (3 4) anterior inferior and posterior inferior pancreaticoduodenal arteries (5)

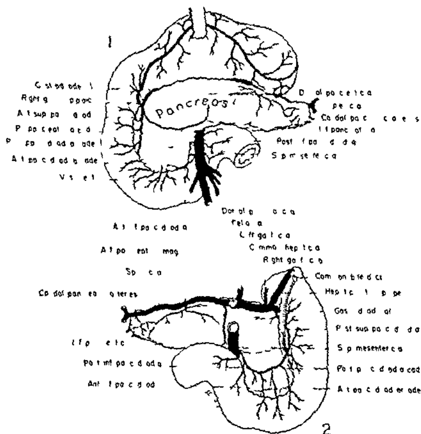


FIGURE 5 Vascular Relations of the Pancreas 1 Anterior View 2 Posterior View (From Olsen L L and Woodbourne R T The vascular relations of the pancreas Surg Gynec & Obst 99 713 1954)

dorsal pancreatic artery (6) inferior pancreatic artery (7) pancreatica magna artery and (8) caudal pancreatic arteries The disposition of these arteries is shown in Figure 5 Originating from the dorsally placed aorta they lie predominantly on the posterior surface of the pancreas only part of the anterior arcade lies on its anterior surface

The head of the pancreas rests in a meshwork of vessels with an arterial arcade on both the anterior and posterior surfaces These arcades or double arterial arches were described by Winslow (1732) Haller (1742 1764) and Wiart (1899) and were called peripancreatic arterial circles by Testut The anterior arcade is formed by the union of the anterior superior and anterior inferior pancreaticoduodenal arteries Woodbourne and Olsen found that in all of 150 specimens the superior artery arose as the termination of the gastroduodenal artery as the latter divides on the anterior surface of the head of the pancreas On the other hand the inferior artery arose from the superior mesenteric artery separately or in union with the posterior inferior artery in 62 per cent of the specimens and took origin from an upper jejunal branch either separately or in common in 36 6 per cent The inferior pancreaticoduodenal arteries arose as a single trunk in 68 per cent of cases and in the remaining 32 per cent there were separate origins for the anterior and posterior vessels The shorter more cephalic posterior arcade is completed by the posterior superior pancreaticoduodenal artery This vessel originates as the first branch of the gastroduodenal artery sinks deeply between the pancreas and duodenum adjacent to the right upper border of the gland to reach the posterior surfaces it spirals around the common bile duct through a large part of its course

Thus there are two arterial arcades one on either surface of the head of the pancreas *These arcades act as shunts between* the hepatic and superior mesenteric arteries Olsen and Woodburne emphasize the vastly different calibers in various specimens ranging from some so small that they are difficult to find to others which are of such large caliber that they lie like ropes over the surface of the gland and may be comparable in size to the gastroduodenal artery They provide vasa recta to the anterior and posterior surfaces of the pancreas Occasionally there is a

separate large direct arterial shunt across the anterior face of the head of the pancreas and when present it is frequently as large as the gastroduodenal artery itself In the study of Olsen and Woodburne it occurred in almost 5 per cent of cases either as a separate and distinct vessel or as a gross enlargement of either the anterior or the prepancreatic arcade The middle colic artery may also lie in this region Normally it is a high branch of the superior mesenteric artery but Olsen and Woodburne found that in 7 4 per cent of cases in their study the middle colic artery or an accessory middle colic artery took origin from pancreatic vessels they appeared either as terminal branches of the gastroduodenal artery as it divided into the right gastroepiploic and anterior superior pancreaticoduodenal arteries or as branches of the dorsal pancreatic artery as it emerged under the neck of the pancreas

The inferior pancreatic artery arises as the left branch of the dorsal pancreatic artery in 84 per cent of cases or exists as a continuation of the left branch of the anterior superior pancreaticoduodenal artery in 10 per cent according to Olsen and Woodburne occasionally (1 3 per cent) it may arise separately from the superior mesenteric artery It runs along the inferior border of the body of the pancreas usually embedded in the dorsal aspect of that border Olsen and Woodburne found a pancreatica magna artery in 64 7 per cent of their dissections and it uniformly coursed on the dorsal surface or was embedded in the gland It is a large pancreatic branch of the splenic artery which enters the pancreas at about the junction of its middle and distal thirds The caudal pancreatic vessels supply the tail of the pancreas in 78 7 per cent of specimens (Olsen and Woodburne) They occur either as a single channel or several arising from the distal end of the splenic artery from the left gastroepiploic artery or from one of the terminals of the splenic artery at the hilum of the spleen

This relatively rich anastomotic pattern of vessels in the pancreas is of course important in pancreatic surgery It may also indicate a relatively good potential for the development of collateral channels in the event of vascular occlusion Schmidt reports that in the brain the intermingling of blood between the right and left halves of the Circle of Willis does not readily take

place *despite a number of vascular connections*, and Healey *et al* have observed a similar lack of commingling of arterial blood between the right and left lobes of the liver Reports of arterial flow patterns in the pancreas are lacking so that this possibility cannot be evaluated at present Nevertheless such considerations are important in determining the susceptibility of the pancreas to infarction following vascular occlusion

The veins of the head of the pancreas have been described in detail by Petren and by *Falconer and Griffiths* The anterior superior pancreaticoduodenal vein empties into the right gastroepiploic vein The anterior venous arcade provides an anterior inferior pancreaticoduodenal vein which terminates most commonly in the uppermost jejunal vein frequently by a common trunk with the posterior inferior pancreaticoduodenal vein or occasionally in the superior mesenteric vein The posterior venous arcade provides a posterior inferior pancreaticoduodenal vein and a posterior superior pancreaticoduodenal vein the former terminates in much the same manner as the anterior inferior vein while the latter is a tributary of the portal vein in almost all cases Petren mentions a vein lying horizontally across the head of the pancreas in a position analogous to the arterial shunt in 50 per cent of cases which he names the anterior medial pancreaticoduodenal vein it empties into the superior mesenteric vein The veins of the neck body and tail show a somewhat lesser constancy although a pancreatica magna vein and caudal pancreatic veins usually correspond in position to the arteries An inferior pancreatic vein empties in about half the cases into the superior mesenteric and in the other half into the inferior mesenteric vein occasionally it empties into the splenic vein A complete dorsal pancreatic vein occurs only occasionally An occasional vein is present which drains the right portion of the neck into the superior mesenteric vein designated by Kirk the pancreatic cervical vein and there are also numerous pancreatic veins which emerge from the dorsal aspect of the gland and empty directly into the splenic vein

d) ***Lymphatic Drainage of the Pancreas*** The lymphatic channels as they emerge from the pancreas extend along the blood vessels On the anterior surface of the tail and body of the

gland the lymphatic trunks pass largely to the superior edge and to the tail to collect in lymph nodes and channels along the splenic artery and vein These trunks and nodes drain primarily into the celiac nodes and lymphatics which have direct connection with the left superior gastric nodes and with the chain of hepatic nodes There are also secondary connections with mediastinal and cervical nodes The lymphatics of the tail are intimately associated with the splenic and the pancreaticoduodenal nodes found at the hilus of the spleen and around the splenic vessels

The anterior surface of the right half of the body neck and head of the pancreas drains into two systems The right suprapancreatic and subpyloric nodes spaced along the superior pancreaticoduodenal vessels connect with both the hepatic and celiac nodes which have a direct continuity with the gastric lymphatics along the right gastric vessels These constitute the upper drainage system

The retropancreatic nodes collect trunks from the posterior and inferior surfaces of the head They follow the posterior superior pancreaticoduodenal vessels to the superior mesenteric nodes and thence to the periaortic chain The middle colic and transverse mesocolic nodes drain the region of the neck and then transmit lymph to the superior mesenteric nodes

The posterior surface of the head of the gland drains directly into all except the pancreaticoduodenal nodes Anastomoses with the duodenal lymphatics are frequent The primary drainage from the posterior surface is cephalad along the common bile duct to drain into the lymphatics along the bile ducts and thence to the hepatic nodes There are also direct lymphatic connections to the posterior abdominal wall and other retroperitoneal structures including the perineural lymphatics And there are also direct lymphatic connections to adjacent organs such as the duodenum Such direct connections may constitute a route by which inflammatory products as from an acute duodenitis might spread to the pancreas

This profuse intermingling of the pancreatic lymphatics with lymphatic channels of other organs and the retroperitoneal tissue (Figure 6) as well as the lack of a restraining peritoneal or fas

cial covering may explain the rapid spread of inflammatory prod ucts from the pancreas to other organs Such a role of the lym

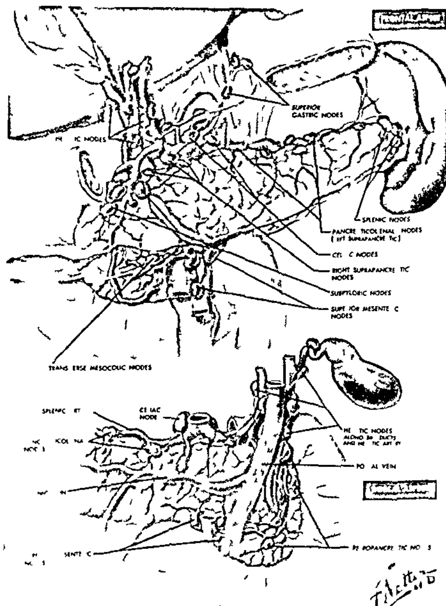


FIGURE 6 Lymphatic Drainage of the Pancreas (Drawn by Netter F From Clifton E E Diseases of the Pancreas *Clinical Symposia* Ciba Pharmaceutical Products Co Vol 9 No 2 Summit N J 1957)

phatics in the distribution of fat necrosis has been discussed in Part I

e) Innervation of the Pancreas The pancreas like other intra abdominal viscera is innervated by both sympathetic and parasympathetic components The sympathetic nerves reach the pancreas through the greater and lesser splanchnic trunks arising from the fifth to the tenth or eleventh thoracic ganglia the major sympathetic innervation appears to be through the greater splanchnic nerve The parasympathetic fibers reach the gland through the vagi and terminate in intrinsic pancreatic ganglia

All of the nerves to the pancreas both afferent and efferent pass through the celiac plexus The sympathetic preganglionic fibers reach the celiac or superior mesenteric ganglia from which postganglionic fibers proceed along the vessels to the pancreas The majority of these nerve fibers accompany the pancreatico duodenal vessels Some fibers accompany the splenic vessels but most of these terminate in the smooth muscle of the capsule and trabeculae of the spleen and only a few in the pancreas

The sympathetic (splanchnic) fibers are believed by some to be distributed primarily to the blood vessels of the pancreas and as stated previously may have their effect on pancreatic secretion indirectly through control of the vascular bed This view is held particularly by Kuntz and by Richins The parasympathetic fibers accompany the vessels as far as the arterioles and then disperse between the pancreatic lobules and around the acini ultimately finding their endings on individual cells These nerves are distributed to both acinar and islet cells and the same fibers may innervate both types of cells The smooth muscle of the duct is innervated by the parasympathetic fibers

Thomas has raised some rather important questions regarding the innervation of the pancreas He points out that nothing is known concerning the relation of the intrinsic pancreatic ganglia to the ganglionic plexus of the intestine and asks Are the pancreatic ganglia derived from the intestinal plexus? Do they have structural and functional relations with the intestinal ganglia in the adult animal? Are stimuli which are conducted through the intestinal plexus also conducted to the pancreas?

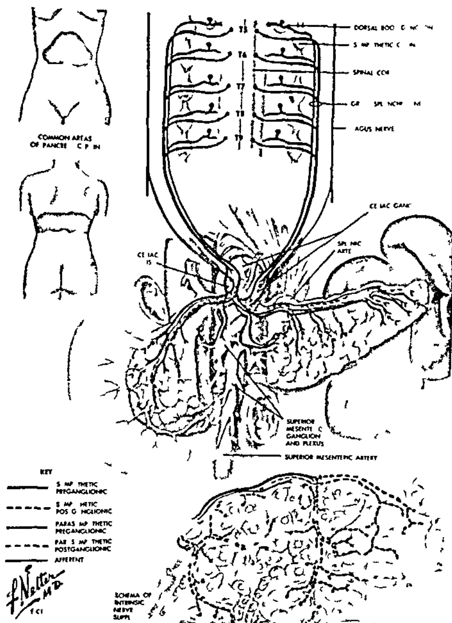


FIGURE 7 Nerve Supply of the Pancreas and the Distribution of Pancreatic Pain (Drawn by Netter F From Clifton E E Diseases of the Pancreas *Clinical Symposia* Ciba Pharmaceutical Products Co Vol 9 No 2 Summit N J 1957)

Can such stimuli influence pancreatic function? Direct nerve connections between the duodenum and the pancreas have been demonstrated by Kuntz and Richins as previously mentioned but much more physiologic experimentation is required to answer these provocative questions They are particularly important to an understanding of the mechanisms of certain of the intestinal phenomena associated with acute pancreatitis mentioned in Parts II and IV

The distribution of pain fibers in relation to the pancreas is also important in accounting for the location of pain in pancreatic disease Afferent pain fibers reach the dorsal root ganglia from the pancreas by traversing the sympathetic route through the celiac ganglia These pain fibers are apparently limited to the greater splanchnic nerves and this concept is supported by the level of the common areas of pancreatic pain and their relief by surgical transection a point which has been dealt with again in discussions of symptoms and therapy The complex innervation of the pan creas is illustrated in Figure 7 including the mode of penetration into the parenchyma

f) *Microscopic Anatomy of the Pancreas* There are three component parts to the pancreas (1) The exocrine portion con sisting of gland forming acinar cells and the associated excretory duct system (2) the endocrine portion composed of the islets of Langerhans and (3) the supporting interlobular connective tissue containing blood vessels lymphatics nerves and excretory ducts



FIGURE 8 Section of human pancreas showing relation of acinar to centro acinar cells Bielschowsky Foot and Mallory azan stains 720 X (From Maximow A A and Bloom W *A Textbook of Histology* 4th Ed W B Saunders Company Phila 1942 p 447)

The exocrine portion is of particular importance here because of its role in the synthesis and secretion of the various pancreatic ferments as presented in Part II The ends of the finest branches of the tree like excretory duct system are called centroacinous cells because they are surrounded by the acinar cells of the secretory parenchyma as shown in Figure 8 The lining cells of the main pancreatic duct consist of a single layer of columnar cells with occasionally interspersed goblet cells Small mucous glands lie adjacent to and empty into the large ducts and along with the occasional goblet cells in the duct provide the pancreatic mucin The walls of the large ducts contain both fibrous connective tissue and elastic fibers but little or no muscle Such a lack of muscle raises doubt as to the validity of spasm of pancreatic ducts as an etiologic phenomenon which may cause pancreatitis The columnar lining of the ducts progressively decreases in height as the latter branch and become smaller so that when ducts enter the lobules of acinar tissue the mucosal lining consists of a single layer of flattened cuboidal epithelium The terminal epithelium of the intercalary ducts is spindle in shape and protrudes into the acinus as the centroacinous cells partially surrounded by the secretory cells of the acinus

The acini of the pancreas tend to be spherical or ovoid in shape their component cells appear blunted and pyramidal in shape and rest on a well defined basement membrane The blunted ends of the cells face inward to form the confining wall of the central lumen The cytoplasm of these cellular units exhibits two zones an inner one adjacent to the lumen containing zymogen or secretory granules and an outer zone free of granules The latter exhibits a variable degree of striation produced by an alignment of mitochondria perpendicular to the basal surface of the cell The relative proportion of these two zones varies with the functional activity of the cells The number of secretory granules increases during fasting and extends into the homogeneous zone When pancreatic secretion flows as during digestion the granular zone diminishes With exhaustion as in continuous secretion only occasional secretory granules may be present but a period of rest restores the granular content of the cells The

nucleus of the acinar cell is spherical or ovoid and basally located A small round paranuclear body is occasionally present in the cytoplasm close to the nucleus and is believed to regulate the production of zymogen granules Canaliculi may be present between acinar cells but these are relatively superficial and do not penetrate to the basement membrane

Groups of acini form primary lobules which are imperfectly separated from other primary lobules by incomplete connective tissue septa Numerous adjacent primary lobules form a secondary lobule and the latter is completely surrounded by connective tissue

The islets of Langerhans are of some importance here because of certain previously mentioned relationships between pancreatitis and diabetes They consist of small collections of cells which lie between acini These clusters are rather sharply defined because they are enclosed in a delicate envelope of reticulated connective tissue and average about 3 mm in diameter The number of islets of Langerhans in adult man may vary from 200 000 to 1 800 000 their concentration varies in different parts of the pancreas Opie has shown that they are almost twice as numerous in the tail as in the remainder of the pancreas and there is a progressive diminution in number towards the head The individual cells tend toward a polygonal shape and the specific granules of the cytoplasm may be demonstrated by special stains On the basis of staining reaction as for example with the Mallory Azan or Masson Methods they have been classified as alpha beta and delta cells The first is believed to contain glucagon a blood sugar raising factor and the second insulin Whether the delta cells are a separate type or a stage in the development of the beta or alpha cells remains to be determined (Maximow and Bloom) In the dog the alpha beta and delta cells constitute 20 75 and 5 per cent of the cells respectively The cells of the islets of Langerhans are typically arranged in a trabecular pattern the meshes of which are occupied by large capillaries

As already mentioned the interlobular connective tissue of the pancreas produces its characteristic lobulation and supports

numerous nerves as well as ducts blood and lymph vessels Fat and fibrous tissue cells are prominent in the interlobular stroma while the stroma about acinar and islet cells is reticular in character

The distribution of blood vessels through this supporting connective tissue is of some significance Beck and Berg have studied the circulatory pattern in the islands of Langerhans and have found that the islands are typically located near the large vessels of the lobules Short direct arterioles supply the island capillaries and there is a free anastomosis between these capillaries and the interacinar capillaries as well as short direct efferent venules draining the island network Thus the islets present as units lying near the central vessels of the lobule having a distinct and separate blood supply independent of the capillaries of the remainder of the lobule except for the free anastomosis between the insular network and the interalveolar rete Beck and Peterson have also emphasized that if an island is large more than one arteriole supplies its network sometimes as many as three arterioles to some of the larger ones These short direct vessels to the islands are in contrast with the longer ones supplying the outlying acinar tissues of the lobules Furthermore since the arterial pressure diminishes directly with the length of the vessel it is higher at the end of a short arteriole than at the end of a longer one This arrangement has a particular significance in relation to the distribution of fibrous scar tissue in the pancreas when the latter is the result of degenerative vascular disease since, as has been pointed out in Chapter 15 in such a process acinar tissue may be replaced but islets may survive and remain functional According to Edmondson *et al* the blood supply is peculiar in another respect In general the vessels are dissociated from the duct system entering the septa between lobules while the ducts enter the lobules and tend to be enveloped by them Only rarely does one encounter a duct and venule or arteriole side by side

The histologic characteristics of the pancreas are not static and undergo progressive changes with age which may exert an influence on the susceptibility to acute pancreatitis Thus Ed

-nondson *et al* have observed that in older people there may be some increase in perilobular connective tissue and fatty infiltration between lobules Bosanquet found some degree of fibrosis in 10 per cent of patients over age 40 Ductal epithelial hyperplasia and atrophy of acini also develop with advancing age The pancreatic vessels are among the most susceptible to arteriosclerotic changes

Chapter 14

THE PATHOLOGIC ANATOMY OF PANCREATITIS

The basic pathologic types of acute pancreatitis were well recognized prior to Opie's treatise on the subject as reviewed in Part I Subsequent to this the only major contribution to the pathologic anatomy of this disease was that of Rich and Duff in which the significance of epithelial metaplasia of ducts and the phenomenon of vascular digestion were presented It seems fair to state that no clearcut relation between the character and intensity of the pathologic changes and the type of etiology has been established Thus there are only three basic pathologic types which under certain circumstances may be interrelated i e edematous suppurative and necrotizing and when the complication of vascular involvement occurs there may be the added component of hemorrhage On the other hand vascular disease may be an initiating factor with pancreatitis superimposed Such considerations have prompted the following pathologic classification of pancreatitis

1 Non hemorrhagic Pancreatitis
   a Acute edematous type with or without fat necrosis
   b Acute suppurative type with or without fat necrosis
   c Acute necrotizing type with or without fat necrosis
   d Pancreatic infarction (primary arterial disease) with superimposed pancreatitis
2 Hemorrhagic Pancreatitis
   a b and c as in 1 with superimposed hemorrhage
   d Pancreatic apoplexy (primary arterial disease) with superimposed pancreatitis

The general gross and microscopic characteristics of these types follow after which attention has been focused upon alterations of specific structural components in the pancreas

a) ***General Gross and Microscopic Characteristics of Acute Pancreatitis*** In acute edematous pancreatitis the organ may be enlarged to about two or three times its normal size it is firm in consistency (indurated) edematous (glassy) and whiter than normal (Figure 9) Hallenbeck *et al* have observed these changes within minutes after injecting bile into the ducts of dogs they may involve the whole organ or may be localized to the head body or tail Fallis gives the relative frequencies as whole of the pancreas 73 1 per cent body 19 2 per cent and tail 7 7 per cent but fails to mention the frequency of involvement of the head alone On the other hand Richman believes the head to be the most frequent site The adjacent retroperitoneal tissues are also usually edematous A cut section through the swollen portion reveals no pus but small areas of fat necrosis may be present hemorrhage is usually absent in transient disease Microscopically edema is evident in the interlobular connective tissue as well as between the acini Neutrophilic infiltration usually varies from mild to moderate and may lie between the acini themselves without appearing to damage the glandular cells or ducts (Figure 10) The neighboring lymph nodes may appear swollen and congested and microscopically show a reactive hyperplasia

As previously noted acute suppurative pancreatitis may result from an intensification of the edematous form or may con



FIGURE 9 Acute interstitial pancreatitis showing swollen indurated pancreas with predominant involvement of the head shown on the left



FIGURE 10 Photomicrograph illustrating marked acute interstitial edema with leucocytic infiltration Vessels also show acute inflammation and thrombosis Approx 100 X Hematoxylin eosin stain

stitute the initial phase At first the gland becomes considerably reddened due to congestion accompanying the increased leucocytic infiltration Pus usually fills inflamed and dilated pancreatic ducts followed by the development of small abscesses The latter may coalesce and enlarge (Figure 11) and later may extend into the retroperitoneal tissues as well as into the lesser sac In three of our cases such extension was responsible for the development of left perinephric abscesses Inflammatory reaction may extend along the pancreatic ducts or directly through the parenchyma Gray sloughs of semi liquid pancreatic tissue or necrotic fat tissue may also be present but as Taylor emphasizes cultures of such areas are often sterile However the same picture may develop as a result of a hematogenous infection or septic embolization and in these cultures may be positive Microscopically large collections of polymorphonuclear leucocytes living and dead are present The ducts are filled with similar collections as well as with cellular debris and inspissated secretion while there is extensive

necrosis of glandular epithelium (Figures 12 13)

Acute necrotizing pancreatitis is also characterized grossly by an enlarged pancreas with soft gray black friable areas of ne



FIGURE 11 Cross section of gross specimen of pancreas showing a large central abscess with cavity formation Along the lower margin are white nodular areas of fat necrosis

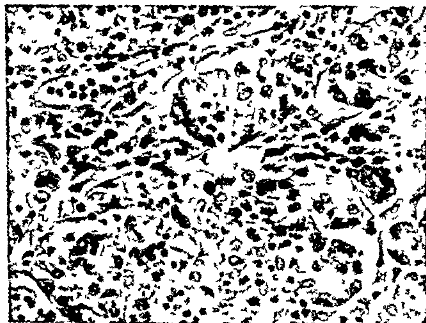


FIGURE 12 Photomicrograph showing diffuse leucocytic infiltration without

destruction of acinar structures This represents an early phase of suppurative pancreatitis Approx 500 X Hematoxylin eosin stain



FIGURE 13 Photomicrograph illustrating a later stage of suppurative pancreatitis with abscess formation Massive infiltration of leucocytes with complete destruction and disappearance of acinar structures is shown in the lower half Dilated ducts containing inspissated secretion are present above the abscess cavity Approx 200 X Hematoxylin eosin stain

crosis Areas of fat necrosis are usually quite extensive and are also present in the mesentery omentum and other sites These appear grossly as firm dry opaque yellow or gray nodules (Figure 14) As the parenchymatous necrosis grows older there is liquefaction and a large cyst may form demarcating necrotic from adjacent living pancreatic tissue Microscopically there is disintegration of parenchymatous elements including islets as well as acini and ducts there is also necrosis of the interstitial tissues Leucocytic infiltration occurs somewhat later than in the suppurative form but may eventually equal the latter in intensity A notable early feature of this lesion is the sharp demarcation between areas of necrosis and normal parenchyma separated only



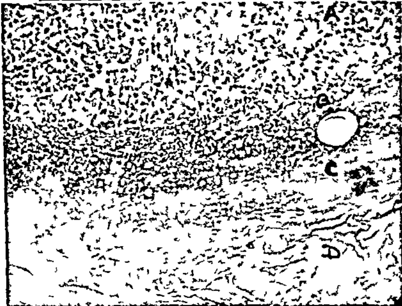


FIGURE 14 Gross specimen showing disseminated fat necrosis of the omentum The fat necrosis is represented by the numerous small irregular white areas in the fatty apron occupying the left half of the figure

FIGURE 15 Photomicrograph showing sharp zonation in an area of parenchymatous necrosis Zone *A* consists of normal parenchyma Zone *B* is a layer of leucocytic infiltration Zone *C* consists of a band of necrotic tissue which in Zone *D* is undergoing liquefaction Approx 100 X Hematoxylin eosin stain

destruction of acinar structures This represents an early phase of suppurative pancreatitis Approx 500 X Hematoxylin eosin stain



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is present and the nuclei are either pyknotic or are undergoing karyorrhexis (Figure 16) It differs then from the focal lesions of necrotizing pancreatitis in that in the latter the outlines of cellular structure have been lost

The necrotic and suppurative lesions of the pancreas may progress to gangrene in which all or most of the pancreas becomes softened and eventually disintegrates The latter may be caused by superimposed occlusive vascular complications such as thromboarteritis or thrombophlebitis or by massive superimposed infection This was found in one of our cases in which all outlines of pancreatic structure were lost and the site of this organ was occupied by irregular separate masses of gray black friable tissue (Figure 17)



FIGURE 17 Gross specimen showing gangrenous pancreatitis The tissue is gray black dry and friable the specimen has broken into several pieces and was removed piece meal from the abdominal cavity

In most instances of the hemorrhagic forms of pancreatitis the extravasation of blood appears to be a secondary phenomenon superimposed on a necrotizing or suppurative lesion As Siler and Wulsin point out hemorrhagic lesions in the pancreas are rarely massive Streaks of blood may lie beneath the peritoneum covering the gland or blood may burrow into the parenchyma along the interlobular fissures producing a marbleized appearance (Figure 18) Fresh hemorrhage may also be present in areas of softening and in cystic areas Microscopically large numbers of red cells or lakes of hemolyzed blood are seen in the interstitial

by a thin zone of leucocytes and congested capillaries or hemorrhage and is thus suggestive of an infarctive process (Figure 15). Sometimes with softening and liquefaction of dead tissue superimposed infection may occur, in which event a local or generalized peritonitis may complicate the disease.

Pancreatic infarct is seen relatively rarely because the necrosis resulting from vascular occlusion is capable of initiating tryptic activity and the definition of the infarct is soon lost, the process becoming indistinguishable from acute necrotizing pancreatitis. When infarction is fortuitously encountered it consists grossly of a soft white area of friable tissue roughly triangular in shape and surrounded by a thin red congested rim. It thus has an appearance similar to infarction of any organ. Microscopically the architecture can be distinguished as ghost structures; cell outlines can be made out but coagulation necrosis of cytoplasm



FIGURE 16. Photomicrograph of a pancreatic infarct. The upper right area consists of normal parenchyma while the remainder of the section shows coagulation necrosis in which cell outlines can still be distinguished. Approx. 100 X. Hematoxylin eosin stain.

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connective tissue and intermixed with areas of necrosis (Figure 19). In some cases hemorrhage is massive and by far the most striking feature of the disease, converting the gland into a solid boggy hematoma (Figure 20). This is a sudden catastrophic event and usually promptly fatal. Such bleeding presumably arises from an open pancreatic artery of medium caliber, but only occasionally can this be demonstrated. Fitz designated this phenomenon as "pancreatic apoplexy" and considered it a separate entity, but more recent authors believe the basic disease to be acute pancreatitis because of the presence of foci of pancreatic necrosis. They consider necrosis to have preceded the hemorrhage and by involving an artery to be responsible for the massive bleeding. Nevertheless, the concept of Fitz has by no means been excluded and remains a strong possibility, particularly in light of the susceptibility of the pancreatic arterial circulation to degenerative vascular disease. Hemorrhage may occur from traumatic rupture of a vessel, rupture of an aneurysm of the pancreatic artery, erosion of the splenic artery by a carcinoma of the pancreas, venous congestion with diapedesis of erythrocytes, venous thrombosis with wet gangrene, suppurative inflammation of an artery wall, with disease altering the coagulability of blood, or as a result of digestive effects on vascular tissues by proteolytic enzymes. Significant hemorrhage was present in 24 of our cases. In 17 of these it resulted from proteolytic digestion of vascular walls, in two from portal vein thrombosis with propagation of thrombosis into pancreatic veins, in two it was due to thrombocytopenia, and in the remaining three it was attributed to intense venous congestion secondary to severe heart failure.

When rupture occurs in a sufficiently large artery, blood is forced directly into the pancreas and the entire structure may come to resemble a large blood clot. The hemorrhage may spread towards the spleen, kidneys, liver, omentum, subperitoneal tissue and the mesocolon. If the barriers confining this flow tear, blood may then be found throughout the abdominal cavity. Even with lesser degrees of hemorrhage ecchymoses may appear in the flank (Turner's sign) or about the umbilicus (Cullen's sign) after the disease has been present for several days. Fallis explains this on



Figure 18 Gross specimen illustrating acute hemorrhagic pancreatitis The duodenum has been divided *to expose the pancreas* and the latter has been cut transversely revealing a large area of hemorrhage in the parenchyma

Figure 19 Photomicrograph of acute hemorrhagic pancreatitis The zonation is similar to that in Figure 15 with the exception that at the lower margin instead of an area of liquefaction necrosis there is a pool of hemolyzed blood



Figure 20 Gross specimen from a case of "Pancreatic Apoplexy" The pancreas has been largely replaced by a boggy hematoma mass

the basis that blood courses from the retroperitoneal position of the pancreas via the abdominal wall and subsequently localizes However, it may perhaps be accounted for on the basis of portal obstruction as in cirrhosis of the liver In one case with umbilical discoloration Cox found the abdominal muscles infiltrated with old blood and in one area a cavity containing dark fluid showing lipolytic activity was encountered With extravasation of blood

of prune juice The development of hemorrhage is usually a serious manifestation carrying a high mortality — 70 per cent according to Morton

In most reports an evaluation of the severity of the disease is based on the intensity of clinical symptoms the mortality rate and the development of sequelae Mortality as such is not an indication of the severity of acute pancreatitis thus Roberts *et al* have graded the intensity of acute pancreatitis in a series of 25 autopsies as severe involving almost all of the pancreas in 72 per cent and marked but involving less than half the pancreas in 28 per cent Hemorrhage was present in 84 per cent and in 64 per cent fat necrosis within the gland was grossly evident Abscess formation was found in half the cases and in four patients these communicated with the lumen of the intestinal tract A somewhat different basis for grading has been adopted here in each case all of the autopsy findings have been evaluated as to the role

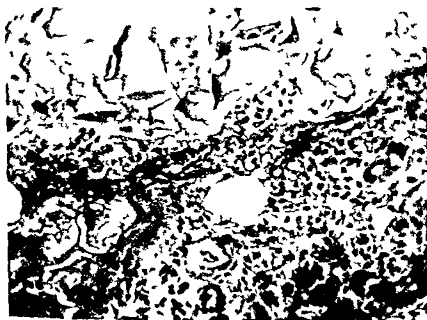


Figure 21 Photomicrograph showing sharp zonation of fat necrosis The area of fat necrosis in the upper part of the figure is separated from the parenchyma by a band of leucocytes Approx 200 X Hematoxylin eosin stain

FIGURE 19 Photomicrograph of acute hemorrhagic pancreatitis The zonation is similar to that in Figure 15 with the exception that at the lower margin instead of an area of liquefaction necrosis there is a pool of hemolyzed blood



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area of fat necrosis as in the preceding figure but in which section has been subjected to microincineration White ash represents foci of deposition of calcium salts Approx 200 X

which they may have played in causing death Thus the pancreatitis was considered the principal cause of death in 17 cases (10 4 per cent) an important contributing cause in 69 (42 3 per cent) and only an incidental finding in 77 (47 2 per cent) Pancreatic and peripancreatic fat necrosis was found in 106 cases (64 1 per cent) hemorrhage in 24 (14 7 per cent) and gross abscess formation in 24 instances (14 7 per cent)

b) *Fat Necrosis* Necrosis of fat appears grossly as dull opaque yellow white areas suggestive of drops of tallow (Figure 14) in cases with icterus they are yellow or dark green Such foci are not raised above the surface and their size may vary from that of a pinhead to about one half inch in diameter They are most abundant in the vicinity of the pancreas although as pointed out they may be found in the retroperitoneal tissues omentum mesentery mediastinum pericardium pleura anterior abdominal wall bone marrow subcutaneous tissues and possibly brain Those that have calcified can frequently be lifted out with the point of a scalpel leaving a shallow depression

Microscopic examination of sections stained with hematoxylin eosin show no nuclei in the foci The network of fatty tissue is filled with a granular substance (fatty acids) which early in the lesion stain red however after the absorption of fluid and combination of the material with calcium the granular material becomes basophilic and subsequently dark blue deposits of inorganic calcium salts appear in the lesions The calcific component is also demonstrable by microincineration (Figures 21 23) Reimann has described a secondary zone of fat necrosis which appears around the first because macrophages arrive in numbers and are also killed Then an inflammatory zone forms around the focus and absorption takes place along with the formation of an encapsulating connective tissue envelope With further liquefaction small cysts may form and with eventual absorption acicular spaces are observed due to solution of the cholesterol crystals in the process of embedding and staining this process is accompanied by the appearance of giant cells eosinophiles and fibro-

FIGURE 22 Photomicrograph showing a sharply demarcated area of necrosis of perilobular fat Approx 200 X Hematoxylin eosin stain

FIGURE 23 Photomicrograph with dark field illumination showing the same



FIGURE 25 Photomicrograph of an artery occluded by an atheromatous embolus The latter contains cholesterol clefts fibroblasts and giant cell reaction similar to that seen in healed fat necrosis A Verhoeff stain displays the elastic lamella of the artery which serves to differentiate this lesion from healed fat necrosis Approx 200 X

present in the circulating blood one would have to assume a concomitant action of trypsin the blood concentration of which is also elevated in pancreatitis plus a local tissue susceptibility in organs not directly affected by the process in the pancreas Perry has demonstrated masses of necrotic fat in the sinuses of lymph nodes in rats which had received pancreatin intraperitoneally and more careful examination of lymph glands in patients with acute pancreatitis might reveal similar lesions According to Scarpelli the bone marrow lesions in human cases vary from microscopic to about 2 mm in size and were found in rib femur and vertebrae As pointed out in Part I, the cerebral lesions described by Vogel may represent a special form of fat necrosis The latter is characterized by numerous widespread focal areas of demyelinization with little neuronal destruction and no inflammation They are

blasts (Figure 24) In this way healing is completed These lesions can be distinguished from postmortem fat necrosis in that in the latter only scattered white spots in and around the pancreas itself are seen with no hemorrhage vascular congestion leucocytic infiltration or calcification Occasionally atheromatous emboli may be mistaken for healed fat necrosis but elastic tissue stains will serve to identify the vascular structure (Figure 25)

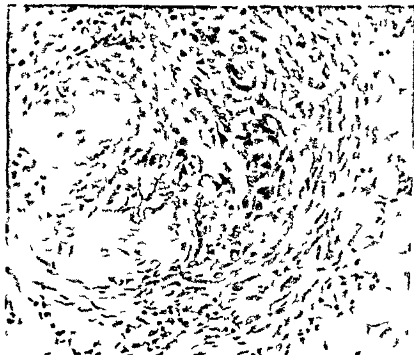


FIGURE 24 Photomicrograph illustrating healing of fat necrosis The amorphous material in the left half of the nodule represents residual necrosis The remaining necrotic material has been replaced by fibroblasts epithelioid cells and an occasional multinucleated cell Approx 200 X Hematoxylin eosin stain

Fat necrosis is apparently due to liberation from the pancreas of lipase and trypsin the latter destroying cellular tissue and the former splitting the fat The dissemination of this process has been attributed by some to the effect of increased serum lipase levels and by others to embolization of necrotic particles as discussed in Part I It appears likely that lipase itself could not cause this reaction since this enzyme in its active form is normally

lost and there remains only a nondescript mass of cellular debris (Figure 15) Cytolytic digestion is also sometimes encountered adjacent to tumor (Figure 26)



FIGURE 26 Photomicrograph illustrating a sharply demarcated zone of parenchymatous necrosis in a pancreas invaded by tumor Tumor cells are small round and darkly staining filling lymphatics adjacent to the area of necrosis Approx 100 X Hematoxylin eosin stain

The recognition of an infarctive process with resulting coagulation necrosis of areas of parenchyma as an important component of the pathologic lesion in acute pancreatitis appears to have been ignored by most students of the disease and attention has been centered almost exclusively on cytolytic digestion by activated enzymes perhaps this is because the latter is rather spectacular and so characteristic of pancreatic inflammatory disease It is important to re emphasize that the pancreas is no exception to the rule that vascular occlusion may produce infarction but that in this organ it may lead in addition to the activation of enzymes which then produce superimposed cytolytic digestion Furthermore even when infarction is not the initiating process

usually perivascular in distribution and suggest that the lipase carried to the brain by the blood has a myelolytic action

Blauvelt has suggested that the multiple foci of subcutaneous fat necrosis which he observed may have been due to the inflamed swollen head of the pancreas compressing the portal vein and causing venous obstruction and pancreatic congestion this process may cause the absorption of microscopic particles of tissues which eventually reach the systemic circulation when portal obstruction is relieved Embolization of this kind has also been suggested by Lynch It might also explain the fat necrosis in the liver observed by Schuller although this phenomenon should occur in most instances of disseminated fat necrosis if this is the route of embolization *Embolization into the lymphatic system* appears equally as likely In the following tabulation the frequencies of some of the more common sites of dissemination of fat necrosis are presented as found by Roberts *et al* as well as in the present series

Site	*Roberts et al (25 Cases)*	*Present Series (163 Cases)*
Pancreas and peripancreatic tissues	64 per cent	65 per cent
Omentum	72 per cent	40 per cent
Mesentery	72 per cent	39 per cent
Visceral peritoneum	24 per cent	17 per cent
Perinephric fat	20 per cent	11 per cent
Retroperitoneal fat	16 per cent	8 per cent
Pelvic fat	*12 per cent*	*11 per cent*
Pleura and mediastinum	12 per cent	0
Brain	0	0
Bone marrow	0	0

c) *Acinar Alterations* The primary change in acinar cells in acute pancreatitis is of course one of necrosis This may be of two types (1) coagulation necrosis and (2) cytolytic digestion As pointed out the first results from occlusion of the vascular supply as with infarction and is usually transient since with release of enzymes cytolysis occurs (Figure 16) It is distinguishable from the latter in that cellular and nuclear outlines remain as ghost structures With cytolysis all cellular characteristics are

creased susceptibility to the disease conferred by such factors as nutritional disturbances uremia and others previously discussed Such dilatation also occurs adjacent to areas of necrosis apparently as a secondary reaction to the pancreatitis In such an event it probably is a manifestation of disturbances of secretory mechanisms In some instances it may be due to ductal obstruction either related etiologically to the pancreatitis or resulting from ductal inspissation of viscid secretion occurring during the progress of the disease

d) *Ductal Changes* The study of Rich and Duff relative to the association of metaplasia of ductal epithelium and acute pancreatitis has served to focus attention on the frequency and significance of ductal alterations Despite the many subsequent studies enumerated in Part I aimed at establishing intrapancreatic ductal obstruction as a causal mechanism the few observations on direct causes of this phenomenon have been negative Thus Rich and Duff could find no evidence whatever that inflammation plays any role in this process nor that it might be due to antecedent obstruction of the duct in which it occurs In this regard they pointed out that in five cases of fibrocystic disease of the pancreas with extreme dilatation of the ducts throughout the pancreas metaplasia was not found in serial sections Furthermore despite metaplasia in many sites in vitamin A deficiency the pancreas appears to be spared Yet elucidation of the causal mechanisms of ductal alterations still loom important since the possibility has not been excluded that they may represent a protective response against some agent which is itself more directly related causally to acute pancreatitis Thus epithelial metaplasia could represent a concomitant response to an irritant capable of initiating pancreatitis even in the absence of ductal obstruction

Two alterations in ductal epithelium in the pancreas have particularly attracted our attention squamous metaplasia and goblet cell transformation Squamous metaplasia was found in 20 9 per cent of our 163 cases of acute pancreatitis and in 17 2 per cent of a group of 111 necropsied cases utilized for a study of sclerosis of pancreatic arteries The second change consisting of a transformation of the columnar epithelium of the large ducts to mucin producing goblet cells was found in 35 6 per cent of the 163

the digestion of vascular walls of interlobular arteries as described by Rich and Duff often leads to thrombosis of such arteries and such a chemically induced thromboarteritis may produce small infarcts in the pancreas which again undergo subsequent cytolysis In this way a process which may initially be focal may become widespread The sharp zonation of necrotic foci in acute pancreatitis is strongly suggestive of such a process and we have noted the presence of such small areas of infarction in several of our cases (Figures 15 and 19)

In acute pancreatitis we have also noted the frequent occurrence of areas of acinar dilatation usually adjacent to but sometimes at some distance from foci of necrosis (Figure 27) There are several possible explanations for this phenomenon Acinar dilatation may be widespread and precede the onset of pancreatitis in such a case it may represent a process associated with in



FIGURE 27 Photomicrograph showing fibrosis and acinar dilatation adjacent to an area of acute inflammation The latter appears along the right margin of the figure Approx 100 X Hematoxylin eosin stain

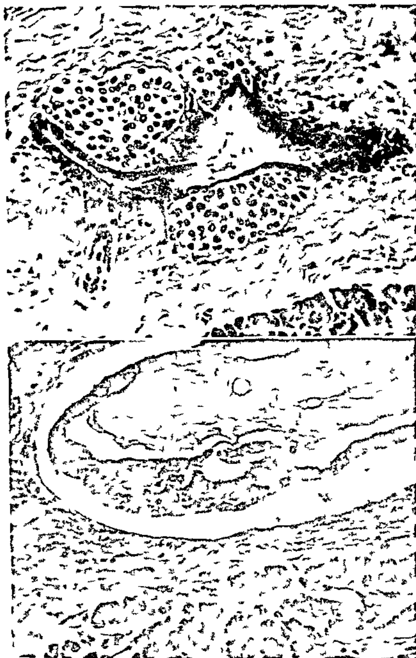


FIGURE 28 Photomicrograph showing squamous metaplasia in a pancreatic duct There is a nodule of metaplastic cells on each side of the duct The upper lobe is covered in part by columnar cells and in part by cuboidal epithelium while over the lower nodule the lining epithelium is thin and atrophic This is an illustration of the fact that the metaplastic epithelium

cases of acute pancreatitis and in 25 2 per cent of the group of 111 cases without pancreatitis

The metaplastic process does not derive from an alteration in the definitive lining epithelium but rather from a proliferation and maturation of scattered elongated cells which lie between the lining epithelium and the surrounding fibrous coat As these cells proliferate and assume epithelial characteristics they push the lining epithelium before them first forming an eccentric mound projecting into the lumen (Figures 28 29 30) Later the metaplastic epithelium may grow completely around the inner surface of the lumen eventually replacing the lining epithelium and even filling and completely obstructing the duct However keratinization of this epithelium as occurs in Vitamin A deficiency has not been observed An analagous metaplasia is seen frequently in the glandular epithelium of the cervix where it is usually attributed in part to chronic irritation and in part to hormonal stimulation As in the pancreatic ducts these metaplastic cells are derived from elongated cells which lie below the lining epithelium and push the latter before them as they project into the lumen

In the case of goblet cell metaplasia the larger pancreatic ducts as shown in the section on microscopic anatomy are lined by columnar epithelium in which there is interspersed an occasional mucin producing goblet cell similar to that which occurs in the epithelial lining of the large bowel These cells disappear as the ducts become smaller and the epithelium lower However in the process of goblet cell transformation the large ducts show an increase in the number of these cells and eventually they completely replace the non mucin forming epithelium These mucin producing cells become large swollen and may produce papillary projections into the lumen (Figure 31) but we have not found complete obstruction as in the case of squamous metaplasia In some cases squamous metaplasia and goblet cell transformation have been found side by side in the same duct

Perhaps more significant than the statistical comparisons of these ductal alterations between populations with and without pancreatitis is the frequency with which they occur in various age groups Such an age distribution of these changes is shown



FIGURE 30 Photomicrograph of a pancreatic duct distended with acute inflammatory exudate The metaplasia here has taken a papillary form Approx 300 X Hematoxylin eosin stain

FIGURE 31 Photomicrograph showing a pancreatic duct the epithelial

is derived from cells beneath the lining of the duct and not from the ductal epithelium Approx 200 X Hematoxylin eosin stain

Figure 29 Photomicrograph of a dilated duct containing inspissated secretion An area of squamous metaplasia is present along the lower lining of the duct Approx 300 X Hematoxylin eosin stain

in the following tabulation based on a careful study of the 111 cases without pancreatitis noted above

Age Group	*No of Cases*	*Metaplasia*		*Goblet Cell Transformation*	
		No	*Per Cent*	*No*	*Per Cent*
0–30 years	16			1	6.3
31–40 years	6	1	16.7	1	16.7
41–50 years	15	3	20.0	3	20.0
51–60 years	24	6	25.0	10	41.7
61–70 years	24	4	16.7	9	37.5
71–80 years	16	3	18.8	3	18.8
81 + years	10	1	10.0	1	10.0

It may be significant that the age distribution curves for both of these alterations parallel closely the age distribution curve for acute pancreatitis as presented in Part I with maxima attained during about the sixth decade followed by a gradual decline One may attempt to relate this peak incidence period to the concept that pancreatitis results when there is an upset of the normal balance between potentially destructive forces and protective mechanisms As regards the former the output of pancreatic enzymes probably diminishes progressively after age 60 as a result of processes of senility which may occur in acinar cells as well as the progressive replacement of the latter as they degenerate by fibrous tissue In part this may also be the result of impaired circulatory function resulting from degenerative cardiovascular disease prevalent after the sixth decade If then one considers the possibility that these ductal alterations represent protective mechanisms it may be expected that their frequency would also diminish when the requirement for protective factors is less because of a diminished production of potentially destructive agents

The process of goblet cell transformation not heretofore described appears to be in the nature of such a protective mech

(Figure 32) Persistent ductal obstruction may lead to the formation of retention cysts and in these pressure of the retained secretion produces an atrophy of the lining epithelium

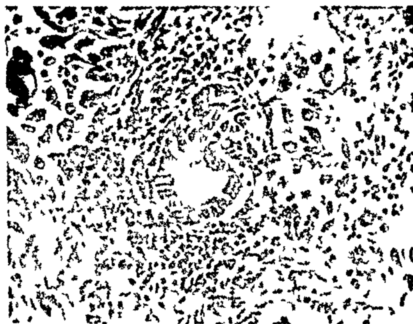


FIGURE 32 Photomicrograph showing replacement of pancreatic parenchyma by tumor *which has begun to compress the duct present in the* center Approx 200 X Hematoxylin eosin stain

Finally inflammation and even rupture of ducts has been observed by many students of acute pancreatitis On an experimental level this has been brought about by the forceable injection of bile and other fluids into the pancreas On a clinical level it has been attributed to the back pressure which may develop in obstructed ducts It evidently can occur even in the absence of either of these causes in which case it appears most likely to be due to enzymatic digestion of the ductal wall (Figures 33 34)

e) ***Vascular Alterations*** There are two important aspects with regard to considerations of structural alterations in vessels as they may relate to acute pancreatitis The first encompasses those degenerative processes which occur independent of pancreatic disease but which may assume etiologic significance in

lining of which has been transformed into tall hypertrophied mucin forming cells Approx 300 X Hematoxylin eosin stain

anism since as has been pointed out in Part II the secretion of mucin may protect the ductal epithelium from autodigestion by activated enzymes Furthermore this process seems to be most marked in that portion of the duct of Wirsung nearest its junction with the common bile duct and therefore in an area where the intrapancreatic activation of ferments is most likely to occur Squamous metaplasia may also be in the nature of a similar protective response rather than a direct cause of pancreatitis although by eventually obstructing ducts it may serve to intensify the disease process Since it occurs in both large and small ducts and in the former we have found it in association with goblet cell transformation it may be that squamous metaplasia is the only protective response of which the lining of the small ducts is capable The increased incidence of these changes in pancreatitis may thus simply reflect an intensification of stimulating agents etiologically related to pancreatitis

The firm establishment of the validity of this concept requires of course considerable further investigation both statistical and experimental However in view of the serious doubt cast upon the significance of pancreatic ductal obstruction alone as an etiology of acute pancreatitis it deserves serious consideration and further study

Dilatation of ducts with inspissation of secretion and pressure atrophy of the lining epithelium has been described by many investigators (Rich and Duff Gaster *et al* Wainwright Popper Edmondson *et al* and others) This change is often accepted as evidence of ductal obstruction as an initiating factor, and indeed in some instances this may be valid On the other hand it appears more likely that with acute pancreatitis necrotic debris is washed into the open ends of ducts along with secretion and their obstruction may constitute a secondary phenomenon (Figure 29) Furthermore in areas of scar tissue formation there may be compression and/or obliteration of ducts as a result of antecedent pancreatitis and dilatation and inspissation of secretion proximal to such obstruction may constitute a cause of recurrent acute disease Tumor can also compress and obliterate ducts

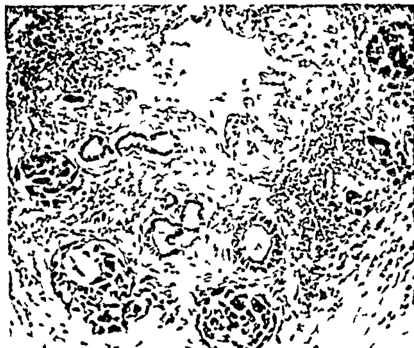


Figure 34 Photomicrograph of a large pancreatic duct showing destruction of the duct lining and wall by acute inflammatory exudate The periductal lymphatics are filled with tumor cells and this is from a case of acute pancreatitis secondary to tumor invasion Approx 200 X Hematoxylin-eosin stain

among non hypertensives Unlike arteriosclerosis in certain other organs it occurs with equal frequency and intensity in both sexes and in Negro and white individuals of comparable age The process in the large pancreatic arteries which course on the surface of the pancreas is comparable in all respects to that described in the splenic artery by Handler Blache and Blumenthal and in these vessels hemodynamic forces play the same important role as in arteries of comparable size supplying other organs (Blumenthal) Fibroelastic plaque formation of moderate degree can be found developing during the fourth and fifth decades of life following which there is a progressive increase in the size and number of such plaques and the appearance of large atheromatous masses Degeneration reduplication and calcification of elastic tissue occur with progressively increasing intensity



FIGURE 33 Photomicrograph of a section through the duct of Wirsung *showing destruction of the duct lining by acute inflammatory exudate* A few mucous glands remain in the submucosa and there are a few small remnants of lining epithelium Approx 100 X Hematoxylin eosin stain

that they may be responsible for deleterious effects on normal protective mechanisms or lead to pancreatic infarct or apoplexy The second takes in those vascular alterations which develop during acute pancreatitis and may have the effect of converting a relatively mild localized process to a more severe and more generalized one

Hranilovich and Baggenstoss have reviewed the literature dealing with arterio and arteriolosclerosis of the pancreas in hypertension but the frequency of similar degenerative vascular disease in non hypertensive cases appears not to be generally appreciated In fact Gruber has attributed to Fahr a statement to the effect that arteriosclerosis of pancreatic vessels occurs only in cases of primary renal atrophy Joshi *et al* have made a study of the arteriosclerotic process in pancreatic arteries in the series of 111 cases previously referred to While this process is somewhat intensified in hypertensive subjects it is also common

elastic lamella is intact and the media appears normal Approx 200 X Hematoxylin-eosin stain

Figure 36 Photomicrograph of a lobular artery of the pancreas containing a fresh thrombus Approx 200 X Hematoxylin eosin stain

from about the fourth decade on and some arteries show dystrophic calcification of muscle fibers similar to that found in the splenic artery

As might be expected hemodynamic forces play a relatively minor role in the development of sclerosis of intralobular arteries and their branches since these operate at relatively low blood pressures and the difference between the surrounding tissue pressure and the intrinsic vascular pressure is likewise small The characteristic lesion in such arteries consists in the development of intimal fibrosis sometimes eccentrically but more often fairly concentric Beneath this the internal elastic lamella remains intact and does not fray reduplicate or calcify until the seventh or eighth decade of life when increasing calcium deposition also occurs in the medial muscle (Figure 35) Thus those vascular alterations which Blumenthal has attributed to hemodynamic forces appear in these intraparenchymal arteries relatively late in life Perhaps the most striking characteristic of the sclerotic process in the intrapancreatic arterial system is the frequency with which thrombi are encountered even in cases without pancreatic disease (Figure 36) The following tabulation records the age distribution frequency of such thrombi in the 111 autopsied cases with a normal pancreas

Age Group	*No of Cases*	*Number with Arterial Thrombi*	*Per Cent*
0–30 years	16	1	6.3
31–40 years	6	1	16.7
41–50 years	15	5	33.3
51–60 years	24	7	29.2
61–70 years	24	9	37.5
71–80 years	16	5	31.3
81 + years	10	8	80.0
Total	111	36	32.4

Thus thrombi in intrapancreatic arteries were found in almost one third of the cases and these were often in various stages of organization so that there was no question as to their ante

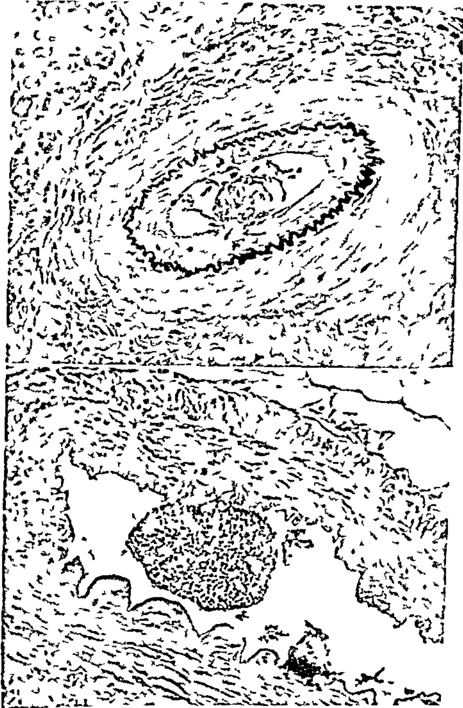


FIGURE 35 Photomicrograph illustrating arteriosclerosis of a lobular artery of the pancreas In the center of the lumen there is an organizing thrombus The intima consists of a circumferential layer of fibrous tissue The internal



FIGURE 38 Photomicrograph showing a dilated vessel with thrombotic lesion of thrombotic thrombocytopenic purpura and marked adjacent acute interstitial inflammation and edema Approx 100 X Hematoxylin eosin stain
FIGURE 39 Photomicrograph showing an atheromatous embolus occluding a

mortem occurrence They were present in arteries of all sizes down to small arterioles Similar thrombi were present with at least equal frequency in capillaries as well as venules Because of the effect of pancreatic enzymes on blood clotting mechanisms is discussed in Part II one cannot but wonder if this process is more intense and more frequent in pancreatic arteries than in other organs but the answer to this question will have to await further study At any rate it would appear that the organization of such thrombi might constitute an important mechanism by which intimal proliferation is accomplished in these arteries In fact Duguid has presented such a process as important in intimal proliferation and plaque formation generally but it would appear to be particularly applicable to intrapancreatic arteries



FIGURE 37 Photomicrograph showing vascular lesion of periarteritis nodosa with slight extension of inflammatory reaction into adjacent perilobular septum Approx 100 X Hematoxylin eosin stain

Other forms of occlusive vascular disease have also been found in our series in association with acute pancreatitis as mentioned in Part I Among these are thrombo embolic phenomena

infarctive process in the pancreas entirely analogous to the usual infarcts in the kidney and spleen in a case with syphilitic aortitis in which vascular occlusion may have occurred on a luetic basis

Most of the foregoing observations have been made in individuals with hypertension in whom intensification of the arteriosclerotic process of the extrapancreatic arteries was in all likelihood also present and may have led to thrombosis Perhaps such thrombi are rarely reported because these vessels are not usually examined as carefully as the coronary cerebral or renal arteries and this may also account for the failure to find aneurysms of the pancreatic vasculature On the other hand Hranilovich and Baggenstoss point out that occlusion of arteries is not always necessary to produce infarction It is now generally accepted that with severe vascular disease congestive cardiac failure shock or other incidents which may lower blood pressure may embarrass the local circulation sufficiently to produce local anoxia with focal necrosis or infarction in the absence of a completely occluded vessel On the other hand even complete occlusion of a major vessel may not lead to infarction if collateral circulation is intact or in the absence of chronic passive congestion of the venous return The frequency of impairment of the venous circulation of the pancreas although stressed by Von Glahn and Chobot many years ago has been surprisingly neglected it is probably as frequent in occurrence as the same phenomenon in the liver where it is more easily recognized

As regards collateral arterial supply it has been pointed out in the section on normal anatomy of the pancreas that there are several avenues of blood supply to the pancreas and thus collateral circulation could be an effective deterrent to infarction in this organ However the integrity of communication between these various major sources of blood is dependent upon the patency of the intralobular arteries through which they may communicate with one another and these are prone to intimal fibrosis with effective narrowing of their lumens

In general the vascular lesions which develop during an attack of acute pancreatitis are easily distinguishable from those of arteriosclerosis or the other specific vascular diseases which have been noted They were first described by Rich and Duff

lobular artery with marked inflammation and destruction of adjacent pan-
creatic tissue. Approx. 200 X. Hematoxylin-eosin stain.

including septic embolization, periarteritis nodosa (Figure 37), and thrombotic thrombocytopenic purpura (Figure 38). In addition, Probstein, Joshi and Blumenthal have reported a series of cases in which acute pancreatitis was associated with embolization of atheromatous material from the aorta to intralobular arteries of the pancreas, where they produced occlusion and acute pancreatitis (Figures 25, 39).

As has been previously suggested, such vascular changes may appreciably diminish the blood supply to parenchymatous elements and thus also the availability of enzyme inhibitors and perhaps other protective substances. This would then have the effect of shifting the balance in favor of the potentially destructive forces. However, the occlusion of vascular elements may play an even more important and more direct role in pancreatitis. Rupture of a severely arteriosclerotic vessel may lead to "pancreatic apoplexy." The development of arteriosclerotic aneurysms with rupture and hemorrhage have been reported in the splenic artery by Michener and Fuge, and they occur occasionally also in the renal artery, but we have been unable to find reports of a similar phenomenon in the pancreatic vasculature. Perhaps a more careful examination of the arterial supply in cases with massive pancreatic hemorrhage would yield examples of this complication of arteriosclerosis; the similarity in the arteriosclerotic process in pancreatic and splenic arteries suggests that it should also occur in the former. Rossle has suggested that vascular lesions would account for the occurrence of fat necrosis if they were more closely looked for, and Hranilovich and Baggenstoss also support this view. As has been noted before, antecedent necrosis of fat cells is required before lipolytic digestion can occur. While tryptic activity may accomplish this, it could also result from occlusion of the vascular supply.

Ischemic infarcts of the pancreas with severe vascular disease have been reported by Klemperer and Otani, Pagel and Woolf, and by Engel. Gruber has discussed a case described by Chiari in which pancreatic necrosis was associated with granular atrophy of the kidneys in a 45-year-old woman, and Rossle has found an

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vascular necrosis due to enzymatic digestion Note particularly the abrupt endings of the internal elastic lamella as it enters into the necrotic area Approx 100 X Hematoxylin eosin stain

FIGURE 41 Photomicrograph showing an area of acute pancreatitis in which the arteries show fibrinoid necrosis Approx 100 X Hematoxylin eosin stain

although Rosenbach had previously mentioned briefly the occurrence of necrosis of blood vessels in the dog s pancreas into which suspensions of streptococci or bile mixed with commercial trypsin had been injected Lowenthal had also previously described medial necrosis of small arteries in the pancreas in human pancreatitis although he stated that the elastic fibers were always perfectly intact and he had never observed their rupture

Since this lesion develops as a result of digestion by enzymes derived from adjacent necrotic pancreas the process begins with a condensation of adventitial connective tissue and an infiltration of leucocytes into this area The muscle fibers of the media then swell their nuclei become pyknotic or karyorrhectic and fluid and leucocytes accumulate between muscle cells The internal elastic lamella first loses its undulations fibrils split off and block like defects develop in it Finally this process results in through and through necrosis which with hematoxylin eosin stain resembles fibrinoid degeneration

While this process starts from the outside and in many instances progresses rapidly inward from all points on the circumference to produce total necrosis of the wall in some instances only segmental destruction is encountered The latter is usually the case when one portion of the circumference lies in an area of acute pancreatitis and the remainder in adjacent unaffected parenchyma (Figures 40 41) In such an event a point of rupture with hemorrhage may develop although thrombosis can occur along the inner margin of the necrotic segment and prevent hemorrhage Rich and Duff found such segmental destruction more frequently in larger arteries while complete necrosis was more common in the smallest vessel the latter were found to develop in as short a time as 24 hours in experimental animals With segmental destruction hemorrhage may extend longitudinally in the media thus producing small dissecting hemorrhages Rich and Duff found thrombosis of necrotic veins more often than



FIGURE 40 Photomicrograph of a lobular artery of the pancreas the upper part of which lies in an area of acute inflammation The darkly staining portion of the wall which extends through its whole thickness represents

Chapter 15

THE PATHOLOGY OF THE COMPLICATIONS AND SEQUELAE OF ACUTE PANCREATITIS

The important complications and sequelae of acute pancreatitis have been discussed in Part I The pathology of these are presented below according to the following classification

a) Cause of Death

b) Fibrosis

c) Chronic Recurrent (Relapsing Pancreatitis) with or without Lithiasis

d) Pancreatic Abscess with or without Sinus Formation

e) Pseudocyst formation

f) Fibrocystic Disease of the Pancreas

a) *Cause of Death* Probably the oldest idea as to the cause of death in acute pancreatitis is the one presented by Fitz that it is due to dehydration and blood loss Morton has stressed the serious nature of hemorrhage an event which according to him carries a mortality of about 70 per cent Elliott and co workers also consider this a serious manifestation and have been able to reduce mortality appreciably with replacement therapy

The concept that a lethal toxin is elaborated by the necrotic tissue has been emphasized by Schmieden and Sebening (1927 1928) despite the fact that Whipple and Goodpasture (1913) had previously demonstrated that this is not a valid concept Subsequently Dragstedt *et al* concluded on the basis of experiments in dogs that sterile autolyzed pancreas is harmless but the presence of anaerobic gram positive organisms similar to Cl welchii in the necrotic tissue is highly lethal presumably due to the elaboration of a toxin

Despite evidence of marked electrolyte imbalance in acute pancreatitis particularly as regards low calcium and magnesium levels this has not been emphasized as a possible cause of death

of arteries but we have found thrombi frequently in both types of vessels

While these lesions are not responsible for initiating pancreatitis since they are an effect rather than a cause of the disease they may nevertheless play a role of considerable importance in producing an extension of the necrotizing process With impairment of the blood supply to adjacent unaffected pancreas by hemorrhage or thrombosis further death of parenchyma may occur and an extensive progression of this process may lead to gangrene of the pancreas

In summary then the first stage of pancreatitis is interstitial edema with mild leucocytic infiltration and in transient pancreatitis the process probably does not progress beyond this point It may however be followed by necrotizing or suppurative pancreatitis and when these processes become massive to pancreatic gangrene This constitutes one course of development of acute pancreatitis On the other hand the disease may not follow this *progression but may be initiated by infarction or hemorrhage* in the pancreas and with the release of enzymes from dead pancreatic tissue cytolysis of marginal parenchymatous and fatty tissue may convert the process into acute pancreatitis and thus mask the initiating events Hemorrhage may in other cases result from the digestion of vascular walls by pancreatic enzymes and thus represent a late rather than an initiating event Certain ductal alterations have been considered as representing concomitant reaction to irritants which may themselves constitute the initiating cause of the disease It is evident that there are still significant gaps in our knowledge of the pathologic anatomy of *acute pancreatitis More careful examination of veins and arteries* may be expected to yield better information than is now available with regard to the frequency of vascular occlusion Careful study of regional and distant lymph glands as well as bones may be expected to provide information as to mechanisms of dissemination of fat necrosis

tissue proliferation could produce a closure of small ducts leading to the formation of retention cysts Oser later recognized that stasis of secretion was an important factor in the production of atrophy and fibrosis and subsequently distinguished two forms of fibrosis a chronic interlobular and a chronic interacinar type The former he considered more common and usually due to obstruction of ducts often leading to marked atrophy of the organ in this form the islets are spared and diabetes is usually not a complication Quenu and Duval have further emphasized the role of long standing stones in the common duct as a cause of interlobular fibrosis The interacinar type in which fibrosis is characteristically present in the centers of lobules Opie apparently considered metabolic because of the frequent association of this change with chronic alcoholism and cirrhosis of the liver Poggenpohl later added still a third type which he called the peri and intraacinar forms In order to avoid confusion in terminology Edmondson *et al* have made the excellent suggestion that the term perilobular be used to indicate increased fibrosis of lobular septal structures and intralobular to indicate fibrosis between acini and fibrous tissue replacement of acinar structures

As we have stated in Part I it is frequently impossible to determine whether fibrosis found in the pancreas at autopsy represents healed acute pancreatitis or an advanced stage of a slow progressive process resulting from a metabolic deficiency vascular impairment or chronic ductal obstruction without antecedent acute inflammation An indication of the frequency with which the latter may occur may be gained from the following tabulation of fibrosis as related to age in the series of 111 cases utilized for the study of degenerative vascular disease Fibrosis has been tabulated as Grade 1 when the perilobular fibrous tissue was only slightly increased and there was no evidence of intralobular fibrosis Grade 2 denotes a moderate increase in perilobular fibrous tissue but still no significant intralobular fibrosis and Grade 3 moderately advanced perilobular fibrosis with some degree of intralobular fibrosis

Edmondson and Berne in particular have studied the development of tetany in cases of acute pancreatitis with depressed serum calcium levels and such an event could constitute a cause of death

A more recent report by Williams serves to re emphasize the fact that acute pancreatic necrosis may be a cause of sudden death with termination occurring only a few hours after onset While the pancreas may show areas of bleeding the latter are usually not sufficiently extensive to account for death on the basis of an exsanguinating hemorrhage Nor is the time period sufficiently long to make superimposed infection and elaboration of a toxin a likely mechanism It would appear that the investigation of possible embolic phenomena might prove fruitful In *this regard it has been shown that in some instances at least* fat embolism may lead to renal and cerebral lesions which may constitute a cause of death in more prolonged cases However it is also possible that with extensive secondary thrombosis in pancreatic venules or with the entrance of particles of necrotic pancreatic and fatty tissue into venules embolization to the pulmonary circulation may also constitute a cause of death

b) ***Fibrosis*** Elman and others have emphasized the fact that in transient acute pancreatitis in which the inflammatory reaction is primarily interstitial there is little or no irreversible damage to acini and ducts and hence no residual fibrosis When acini and ducts are irreversibly damaged or destroyed as in the more severe forms of acute pancreatitis replacement of these structures is by fibrous tissue However fibrosis of a more gradual and progressive character can occur with circulatory impairment metabolic disease or with ductal obstruction the latter type being recognized since the important observation of von Mehring and Minkowski that ligation of the main pancreatic duct leads to eventual fibrous replacement of the exocrine portion of the pancreas while sparing the islets of Langerhans

Friedreich first recognized the basic patterns of connective tissue change in the pancreas He emphasized that hyperplasia of the interacinar connective tissue produces atrophy and disappearance of the parenchyma and also observed that connective

would appear to implicate vascular factors although metabolic and obstructive factors may also have contributed in some of these cases Furthermore as Hranilovich and Baggenstoss have pointed out progressive ischemia may have the effect of producing foci of atrophy with secondary replacement by fibrous tissue A common cause of such ischemia may be venous stasis which occurs at the periphery of lobules where perilobular fibrosis

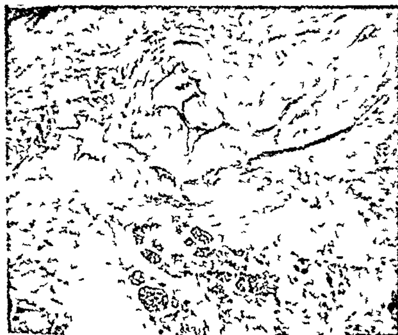


FIGURE 43 Photomicrograph showing extensive replacement of lobular tissue by fibrosis The large artery contains an organized thrombus Approx 100 X Hematoxylin eosin stain

Figures 42 and 43 are from different areas of the pancreas of a 67 year old male who was first admitted to the hospital 24 years prior to death At that time he had symptoms which were thought to be due to cholecystitis and a cholecystectomy was performed He continued to experience abdominal pain and five years later an exploration of the common duct was carried out but no stones were found Over the next 17 years he had nine hospital admissions for abdominal pain and each time an elevation of the serum amylase was found He never developed diabetes signs of deficiency of exocrine function or calculi of the pancreas He finally died as a result of a cerebrovascular hemorrhage

Age Group	Number of Cases	Grade 1		Fibrosis Grade 2		Grade 3	
		No	Per Cent	No	Per Cent	No	Per Cent
1–30 years	16	12	75.0	4	25.0	..	
31–40 years	6	3	50.0	3	50.0		
41–50 years	15	4	26.7	11	73.3		
51–60 years	24	4	16.7	15	62.5	5	20.8
61–70 years	24	2	8.3	14	58.3	8	33.3
71–80 years	16	2	12.5	9	56.3	5	31.3
81 + years	10			6	60.0	4	40.0
Total	111	27	24.3	62	55.9	22	19.8



FIGURE 42 Photomicrograph showing replacement of lobular tissue by fibrosis Scattered compressed ducts and acini remain Approx 100 X Hematoxylin eosin stain

It is apparent from the foregoing table that there is an increase in the proportion of cases with fibrosis of Grades 2 and 3 with advancing age and that after age 60 approximately one third of the cases show fibrosis of Grade 3 The progressive increase in fibrous tissue as well as the progressive increase in numbers of cases showing fibrosis of Grades 2 and 3 with age

way the process may be self perpetuating until the lobule is completely destroyed The cellularity and maturation of the connective tissue varies with the age of the lesion thus there are more fibroblasts in younger lesions and more collagen in older ones Old lesions may also contain varying quantities of elastic fibrils (Figure 44)

c) *Chronic Relapsing (Recurrent) Pancreatitis with or without Lithiasis* This condition has been variously described as pancreatic induration pancreatic cirrhosis or atrophic cirrhosis insofar as its gross pathologic characteristics are concerned The surface of the pancreas is irregularly nodular with frequent adhesions to adjacent organs There is increased resistance to cutting depending on the degree of fibrosis Dilation of ducts is common and easily appreciated in the gross specimen and these ducts may be filled with thick gray fluid resembling jelly Reduction in size of the pancreas may or may not occur depending upon whether atrophy and end stage fibrosis or fibroplasia and inflammation predominates The gland may even exceed the normal weight If terminal acute pancreatitis is superimposed foci or parenchymatous and fat necrosis may be seen and abscesses focal hemorrhages and pseudocyst formation may be present In addition compression of the splenic vein or common duct by fibrous tissue may be encountered

The microscopic characteristics of the fibrous tissue reaction has been described in the previous section There may be destruction of portions of lobules or of entire lobules during an acute attack When the latter is finally healed all that may remain are a few acini an occasional duct and perhaps an islet The acute inflammatory reaction is replaced by lymphocytes and in the event of hemorrhage many hemosiderin laden macrophages Endo and perineural infiltration of lymphocytes with degeneration of ganglion cells has been described by Mallet Guy and de Beaujeu Comfort *et al* and others The increased susceptibility of the tail of the pancreas to recurrent disease has been attributed to the fact that in this portion of the pancreas only one duct is present (Savy *et al* Soupalt Brocq and Maginiac) so that in the event of obstruction secretion cannot be routed through the duct of Santorini

begins Such stasis appears to be as frequent in the pancreas as in the liver in patients with congestive heart failure Hranilovich and Baggenstoss further stress the fact that the presence of normal appearing islets of Langerhans in such areas of fibrosis is an indication that there was no antecedent necrosis or infarction The overall pattern of fibrous tissue proliferation is however similar to that reported by Edmondson *et al* as characteristic of that seen in chronic relapsing (recurrent) pancreatitis Perilobular fibrosis occurs first and is most marked accentuating the lobular pattern From the perilobular septa fibrous bands penetrate into the lobules breaking them up into several smaller ones and with continued branching greater separation of acini is accomplished (Figure 42) Eventually a complete lobule may be replaced by fibrous tissue (Figure 43) In addition to ischemia which may initiate the process the fibrous tissue may further compress acini and contribute to their atrophy in this



FIGURE 44 Photomicrograph showing an area of pancreatic parenchyma completely replaced by scar in which there is extensive elastosis Approx 100 X Verhoeff stain

escape of pancreatic juice via the duct of Santorini Solitary stones are usually located in the main ducts while in cases with multiple stones small calculi are often found in addition in small ducts and even acini (Figure 45)



FIGURE 45 Atrophy of the pancreas caused by calculi in the pancreatic duct The pancreatic duct is greatly dilated and contains many calculi (From Bell E T *A Textbook of Pathology* Lea and Febiger Phila 1956 p 630)

Some idea of the processes of formation of calculi may be obtained from the microscopic characteristics of small concretions These are of two types The first consists of masses of inspissated debris and desquamated epithelium some of which may contain calcium In the second type tiny crystals of calcium salts are widely dispersed in the debris

Calculi may vary from microscopic sized particles to sand like grains to a walnut size They are rarely smooth more frequently nodular mulberry shaped or cylindrical sometimes branched occasionally faceted As a rule they are white in color but some are brown If the organic content is high they are soft but more often they are hard In the latter there is an organic framework between which there are deposits of calcium carbonate and phosphate

d) *Pancreatic Abscess* Local areas of pus formation are not nearly as frequent in the pancreas as cytolytic necrosis which may undergo liquefaction When pus is present bacterial contamination is considered to have occurred Most often the pus

Alterations in the ducts usually include dilatation hyperplasia and squamous metaplasia The hyperplasia includes both an increase in the number of ducts as well as an increase in the height of the epithelial lining cells The increase in the number of ducts follows lobular destruction in much the same manner as bile duct proliferation in the liver follows the destruction of functional elements However unlike the analagous situation in the liver the process in the pancreas does not appear to predispose to malignancy

Vascular sclerosis is usually severe In addition to the expected degree of arteriosclerosis as related to the age of the patient there is undoubtedly a healed inflammatory thromboarteritis as well as healed lesions of vessels partially destroyed by the pancreatic enzymes during acute attacks

Some islet destruction very likely occurs in most instances although the degree is difficult to evaluate because of the variation in numbers in different parts of the pancreas However remnants of islets may remain in areas of fibrosis and thus indicate their involvement in the inflammatory process

Lithiasis of the pancreatic ducts has in our experience been a rare occurrence only three in over 3000 necropsies (0 1 per cent) In the study of Edmondson *et al* this lesion was found in 0 05 per cent of autopsies in a twenty one year period and in 0 33 per cent in a subsequent group of 3000 autopsies Bell has found calculi in only eight of 75 986 autopsies (0 01 per cent) Perhaps more significant is the frequency of such ductal calculi in chronic relapsing pancreatitis if one combines Bells data with those of three other investigators referred to in his report the incidence in recurrent disease is 36 in 145 cases (25 per cent) In the study of Edmondson *et al* the stones were multiple in 20 cases and solitary in six The most common site is in the duct of Wirsung about 2-4 cm from the ampulla of Vater and Edmondson *et al* suggest that they may become impacted at this point after being carried down from the body or tail They point out that the significance of this location lies in the fact that the stones are close enough to the common duct so that biliary obstruction may supervene and that this location allows for the

the duodenum in the head of the pancreas, along the lesser curvature of the stomach, and in the root of the mesocolon. According to Berkan, the three most common locations in order of their frequency are (1) behind the gastrocolic ligament and presenting between the stomach and the colon, (2) under the gastrohepatic omentum and presenting between the stomach and the liver, and (3) between the layers of the transverse mesocolon either behind the colon or below it (Figures 46, 47, 48). Location is important in therapy, since it determines the choice of internal drainage as described in Part V.

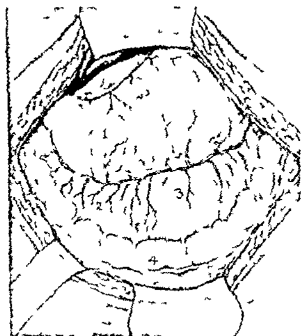


FIGURE 46. Cystic mass shown in its relation to the stomach and the large bowel. 1. Stomach in transparency, showing outline of cyst. 2. Gastrocolic ligament. 3. Cystic mass under gastrocolic ligament. 4. Transverse colon. (From Wilford, E. C., Arnold, C. H., Ho, K. I., and Shen, H. H.: Pancreatic fluid accumulation subsequent to trauma. *J. Internat. Coll. Surg.*, 14:280, 1950.)

As Mahorner and Mattson have suggested, the histological distinction between a true and a pseudocyst is based on the absence of an epithelial lining in the latter. However, at some point

exists as multiple small abscesses in a swollen red gland Such abscesses may enlarge and eventually form adhesions with adjacent duodenum point towards this segment of the intestinal tract and eventually rupture into it to form a sinus tract They may also rupture into the lesser peritoneal sac where a pseudocyst may be formed

Microscopically the abscess usually has a thin fibrous capsule and contains masses of leucocytes both living and dead necrotic tissue albuminous fluid and occasionally some blood

e) ***Pseudocyst*** Pseudocyst may result when there is massive hemorrhage due to rupture of a pancreatic vessel traumatic rupture of the pancreas with active pancreatic juice and blood pouring into the omentum liquefaction necrosis of the pancreas with extension into the omentum or rupture of a pancreatic abscess as noted above Because of its posterior position the fluid materials which accumulate from the preceding events fill the pancreas and reach forward along the line of least resistance into the omental bursa At times the only recognizable features consist of necrotic opaque yellow brown remnants of the anterior wall of the pseudocyst and numerous foci of fat necrosis Secondary infection presumably from the bowel may cause a filling of the cavity with pus or pus may be present initially if the pseudocyst is derived from an abscess The older the cavity the better the encapsulation by granulation tissue and the better developed is the cyst Adhesions to surrounding tissues develop and the cyst content is transformed into a cloudy thick gray yellow fluid sometimes admixed with blood but containing no cells or nuclei The sac enlarges as long as the digestive action of pancreatic juice persists suppuration continues or hemorrhage occurs Finally the process becomes stationary During the development however a fibrinopurulent peritonitis deep abscess formation or erosion of neighboring arteries can occur During the developmental stages diastatic proteolytic and lipolytic activity of the pseudocyst content can be demonstrated

Adams and Nishijima found pseudocysts located between the stomach and liver posterior to the stomach and pressing against the gastrohepatic omentum along the lesser curvature of

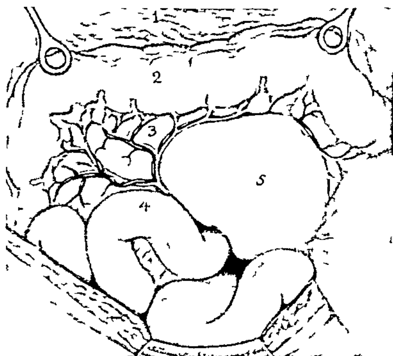


FIGURE 47 Situation of pancreatic cyst the transverse colon being reflected 1 Greater omentum 2 Transverse colon reflected 3 Transverse mesocolon 4 Jejunum 5 Cyst seen through thinned-out mesocolon (From Wilford E C Arnold C H Ho K I and Shen H H Pancreatic fluid accumulation subsequent to trauma *J Internat Coll Surg* 14 280 1950)

in their wall most pseudocysts have a communication with the duct system or secretory tissue of the pancreas and examination of this area may reveal epithelial tissue The latter lies within the layers of the cyst wall and show ductal or acinar structure In general however the cyst wall consists either of granulation tissue or of more mature fibro-collagenous elements (Figure 49)

The term pseudocyst has also been applied by some investigators to designate the small cysts formed within the confines of the pancreas in chronic relapsing (recurrent) pancreatitis These probably represent retention cysts derived from ducts obstructed by fibrous tissue compression Initially the cuboidal epithelial lining becomes compressed by fluid pressure from within and this process may progress to complete atrophy of epithelium so that the cyst lining may ultimately come to appear similar to that seen in true pseudocyst

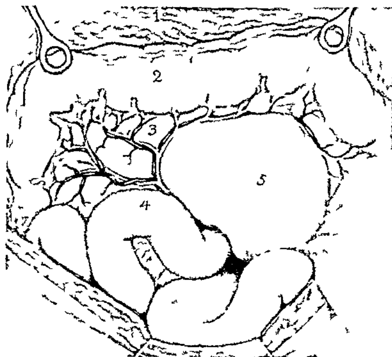


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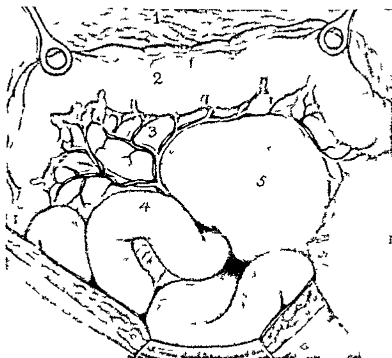


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FIGURE 48 Gross specimen showing a pancreatic pseudocyst held open by applicator (arrow) showing smooth inner surface

FIGURE 49 Photomicrograph of a portion of the wall of a pseudocyst showing absence of an epithelial lining (upper surface) The wall is composed solely of fibrous tissue Approx 300 X Hematoxylin eosin stain

f) *Fibrocystic Disease* This picture is seen in uremia nutritional disturbances hepatic disease high intestinal obstruction or chronic ulcerative colitis Whether or not in these diseases there is an increase in the viscosity of the pancreatic secretion remains to be determined At any rate with these changes there appears to be an increased susceptibility to bouts of acute pancreatitis which may serve to intensify these pathologic processes

Grossly the pancreas may not be remarkable except to be firmer and thinner than normal There is however an infiltration of fat and fibrous tissue between the lobules and an unevenness in the size of lobules The pancreatic duct is usually patent Microscopically many acini and ducts are dilated and contain inspissated eosinophilic secretion The pancreatic parenchyma is atrophic and scanty in advanced cases with a relative increase in fibrous tissue The stroma is frequently infiltrated with lymphocytes and mononuclear cells The ductal epithelium is often flattened and the inspissated material within the lumens may be laminated and sometimes calcified The islets of Langerhans appear relatively unaffected

Cystic fibrosis of the pancreas in infants and children is generally considered a disease entity in itself and not a complication of recurrent pancreatitis although it has many pathologic features in common with the latter Nevertheless there are pathologic changes in this disease which suggest that there may be superimposed inflammatory reaction which may contribute to the end stage picture For this reason it is included here although we recognize the fact that cystic fibrosis of the pancreas is not initiated by acute pancreatitis

SUMMARY

Thus the significance of the anatomic location of the pancreas with reference to the pathology of pancreatitis rests in part on its relation to adjacent organs which determine the extension of inflammatory reaction to the latter and in part to its vascular relations Its retroperitoneal location is such that when inflammatory exudate extends beyond the confines of the pancreas such phenomena as perinephric and retroperitoneal abscesses may result and this location also determines the sites of pseudo

cyst formation Vascular drainage into the liver may account for certain of the hepatic complications pointed out previously In general the arterial distribution is of such a nature as to afford the potential for an adequate collateral blood supply and this may serve to diminish the frequency of infarction despite the high rate of occurrence of vascular thrombi Its lymphatic drainage probably determines in part the sites of dissemination of fat necrosis The pathologic alterations in the pancreas are a reflection of the effects of the activated enzymes of this organ when protective factors have lost their effectiveness Important considerations with regard to such loss of protection are the alterations in the ducts and vessels The ductal alterations probably represent responses of a protective nature when the activation of enzymes is intensified and may not in the first instance constitute a cause of the disease On the other hand degenerative vascular disease may represent an effective mechanism whereby protection is lost The digestive action of enzymes on the vascular structures of the pancreas is peculiar to this organ and this disease It may serve to convert a limited process into a fulminating one

Healing in pancreatitis is similar to that in other organs and is primarily by fibrosis although ductal proliferation similar to that seen in the liver is also encountered in the pancreas However the fibrosis if sufficiently pronounced may serve to obstruct ducts and the healing of vascular lesions serve to diminish the blood supply These processes then leave the pancreas vulnerable to further attacks Lesions similar to healed pancreatitis have been observed with other diseases as listed above and in this an increased vulnerability to acute attacks also appears to exist The pathologic alterations of recurrent pancreatitis are thus simply the summation of acute healing and healed processes Calculus formation in ducts is probably in the first instance not a complication of an acute attack but is more likely due to unrelated disease such as hyperparathyroidism However once formed calculi may serve to obstruct ducts and precipitate acute attacks

Thus the pathologic alterations may reflect the effects of both attacking and protective forces as described in Part II

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PART IV

THE CLINICAL MANIFESTATIONS OF PANCREATITIS

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Chapter 16

THE CLINICAL MANIFESTATIONS OF ACUTE PANCREATITIS

Pratt quotes Wardell as stating in 1871 that No symptoms are pathognomonic of pancreatic disease an assemblage of symptoms indicates the probability of its lesions It remains equally true that no symptoms or physical signs have been discovered that are pathognomonic of either acute or chronic pancreatitis It should now be evident from what has been presented in the foregoing parts that despite textbook descriptions of classical signs and symptoms there is to be expected considerable variability in the intensity of the clinical manifestations ranging from cases with vague symptoms and a mild course to severe fulminating disease In general however there appears to be a correlation between the intensity of the disease process and the severity of symptoms The milder forms usually exhibit some digestive distress mild abdominal pain and some nausea in these the diagnosis may rest wholly on the demonstration of an elevated serum or urine enzyme level such as amylase by an alert observer At the other extreme the disease may run a severe fulminating course with early death and the diagnosis be made only at autopsy

Often what appears to be an initial mild attack in an otherwise healthy subject may on careful questioning prove to be one of a series of similar attacks some of which have been of such a mild subclinical character that medical aid was not sought Frequently an important clue as to the nature of the disease process is a history of onset following a heavy meal or trauma to the abdomen or alcoholic excess The important clinical symptoms are pain nausea and vomiting abdominal distention and sometimes shock Moderate fever transient icterus and occasionally evidence of gastrointestinal hemorrhage are also present The characteristics of these symptoms are detailed below

date is present there is also irritation of nerve endings in the serous lining

Typically pain arises suddenly in the upper abdomen most frequently in the mid epigastric region but sometimes in the right upper quadrant with radiation to the back or left flank Pain may arise in the region of the gallbladder and simulate cholecystitis but if it radiates to the left lumbar area and to the left flank it points to irritation in the lesser peritoneal cavity and thus *strongly suggests pancreatitis Less commonly the pain radi* ates transversely in the epigastrium or becomes generalized in its distribution In the two tables below a comparison is presented of the frequency of the various primary sites of pain as well as sites of radiation as detailed in several studies It is evident from these data that there is no sharp distinction between what is con sidered the initial site of pain and that believed to be due to

PRIMARY SITE OF PAIN IN ACUTE PANCREATITIS

	Bockus et al		*Taylor*		*Roberts et al*		*Present Series*	
Site	*No*	*Per Cent*	*No*	*Per Cent*	*No*	*Per Cent*	*No*	*Per Cent*
None	2	2					11	7
Epigastric	50	53	60	54.5	11	44	22	13
Upper abdom	4	4			7	28	38	23
RUQ	19	20	18	16.4	3	12	37	22
LUQ	9	10	2	1.8			11	7
Lower abdom	5	5	8	7.2	4	16	17	10
LLQ	5	5	15	13.6			27	17

DISTRIBUTION OF PAIN EXPERIENCED AS RADIATION FROM INITIAL SITE

	Bockus et al		*Taylor*		*Roberts et al*		*Present Series*	
Site	*No*	*Per Cent*	*No*	*Per Cent*	*No*	*Per Cent*	*No*	*Per Cent*
None	23	25			10	10	57	35
Upper abdom	10	11						
RUQ	5	5						
LUQ	2	2			3	12		
Lower abdom	4	4						
RLQ	1	1						
LLQ	2	2	1	0.9				
Back	43	48			10	40	58	36
Diffuse abdom	2	2	48	43.6				
Shoulders			12	10.9	2	6	18	11
Left chest			1	0.9			7	4
Right flank			1	0.9			7	4
Both flanks							16	10

1) *Signs and Symptoms* *Pain* is the most prominent and most constant symptom of acute pancreatitis It was a major symptom in 96 per cent of the cases studied by Bockus *et al* and in 93 per cent of the cases in the present series despite the fact that in slightly less than one half of the latter the pancreatitis was only an incidental disease The severity of the pain is often considered a rough index of the degree of pancreatic damage In mild cases of transient pancreatitis it may consist of no more than slight epigastric distress and as the pathologic lesion progresses the pain usually increases until it may attain excruciating proportions Characteristically with severe disease the pain is steady unrelenting and uninfluenced by vomiting with only slight relief obtained with morphine and other analgesics as detailed in Part V In the average mild case the pain begins to subside after 48 hours On the other hand when pain remains unabated or increases beyond this period it is usually an indication of progression to a more serious form of pancreatitis or to the development of one of the early complications detailed in the following section

The intensity of the pain is often described as sudden agonizing persistent colicky or stabbing but as Taylor points out it would be misleading to expect this in every case As a rule about one fourth of the cases in most series including the present study are of such a severe type and in the remainder it ranges from intense but somewhat less severe to a few in which a gnawing or burning character is described This pain may be continuous or paroxysmal in character Taylor is of the opinion that the intensity depends on one or more of the following factors (1) The degree of obstruction of the ampulla of Vater (2) The extent of pancreatic involvement (3) The amount of pancreatic hemorrhage (4) The quantity of serous exudate (5) The extent of involvement of retroperitoneal tissues (6) The concomitant biliary pathology especially if acute and (7) The presence of localized or generalized peritonitis More specifically edema and swelling of the pancreas results in stretching of its capsule It also produces compression of the common duct if the head is involved with resultant impairment of bile drainage In addition there is pressure on the celiac plexus If a large amount of peritoneal exu

the upper lumbar and lower thoracic sympathetic chains In addition to these pathways there may be direct connections between the viscera and the sympathetic chains which do not traverse the celiac plexus Upon reaching the ganglionated chains individual visceral pain fibers leave the chains at the same or at higher levels by way of the rami communicantes leading to the posterior sensory roots of the cord This distribution then can account for pain over the abdomen thorax back and lumbar regions

Nausea and vomiting often promptly follows the pain These events were present in 69 (42 3 per cent) of cases in the present series and in 80 9 per cent in Taylor s study In the mildest cases only nausea may be present When vomiting occurs it is of a reflex nature and may be severe and persistent In such cases there is a continuous gagging retching or vomiting of bile despite an empty stomach and this may lead to dehydration and exhaustion of the patient Vomiting ceases within 48 hours in mild cases Taylor points out that the absence of bile in the vomitus may constitute a sign of great value in the diagnosis of the presence of ampullary obstruction If the patient has not vomited aspiration of the duodenal content may serve as a means of determining the patency of the common bile duct

Abdominal distention is a rather common symptom of acute pancreatitis In many cases it is due to the development of paralytic ileus an event which usually occurs on or about the third day of an attack and thus is usually accompanied by constipation and bloating of the epigastrium As the ileus and distention become more pronounced the vomitus increases in amount and assumes the appearance of intestinal content as in other forms of intestinal obstruction Even in cases without paralytic ileus constipation is a common event in acute pancreatitis and some abdominal distention may result from this alone Distention is also due to the accumulation of exudate within the peritoneal cavity

Shock is present in the more severe types of the disease and the drop in blood pressure is often accompanied by cyanosis and dyspnea presumably due to associated coronary insufficiency and myocardial anoxia It may be dramatic in its development in the most severe cases and in those in which pancreatitis is followed

radiation hence sites recorded as areas of radiation by some investigators are considered as part of the initial pattern of distribution by others Nevertheless the marked variability in the distribution of both the primary and radiating sites of pain presents problems in differential diagnosis dealt with later in this section

Taylor attributes the distribution of pain to the following (1) Associated biliary disease (2) Rapid inflammatory swelling of the pancreas with stimulation of the nerves of the celiac plexus and posterior parietal peritoneum (3) Copious exudate in the peritoneal cavity producing marked irritation of the parietal peritoneum (4) Increased pressure within the pancreatic duct and (5) Location of trauma if present Bliss *et al* from their experimental study of pain patterns produced by electrical stimulation of various parts of the pancreas found that pain originating in the head of the pancreas localizes to the right of the midline from the xiphoid to just below the umbilicus Pain starting in the body is referred to the midline and pain arising in the tail is felt to the left of the midline from the xiphoid to the groin Radiation of pain to the back may occur from all parts of the pancreas Chapman *et al* have shown that pain evoked by experimental stimulation of the common bile duct and upper small bowel is the same as the pain of pancreatitis This finding is explained on the basis of a common efferent nerve supply in the greater splanchnic and lower thoracic sympathetic nerves

This broad and varied distribution of pain is not surprising when one recalls the many nerves in the region of the pancreas Ray and Console have emphasized the fact that most nerves supplying the abdominal viscera including the pancreas traverse the celiac plexus which includes the celiac and mesenteric ganglia Pathways for connections between the celiac plexus and the paravertebral gangliionated chains include the splanchnic nerves and a plexus about the thoracic aorta thus accounting for referred pain to the chest Of the splanchnic nerves by far the most constant *in structure* and probably also the most important in transmitting afferent impulses is the greater splanchnic on each side The lesser and least splanchnic nerves have a variable anatomic
... man which generally connect the celiac plexus to

or by the development of large collections of exudate in the greater and lesser peritoneal cavities The loss of fluid by these various routes may amount to several liters in the course of even a single day Another contributing factor to shock may be the accumulation of toxic products liberated by the damaged tissues Taylor sums up the causes of rapid shock and collapse as possibly due to the following (1) Pressure of blood on the semilunar ganglia and celiac plexus (2) Absorption of toxic products derived from proteolytic digestion in the pancreas (3) Reflex disturbances mediated through the nerves in the region of the pancreas (4) Severity of the hemorrhage and (5) Stripping of the parietal peritoneum of the posterior abdominal wall by dissecting retroperitoneal hemorrhage

Fever is usually either mild or absent and chills do not occur as a rule according to Siler and Wulsin Bockus *et al* found the median temperature in their series to be 100 5°F While 20 per cent of their cases exhibited a normal temperature it was above 102°F relatively infrequently In the present series about half the cases showed mild temperature elevations and it was found to be above 102°F in 17 instances (10 4 per cent) Siler and Wulsin further point out that with impending or actual shock the temperature frequently falls to below normal levels

Icterus in the absence of evidence of biliary tract disease may be encountered Richman states that transient jaundice of this type is present in about 25 per cent of cases and Musser has observed it in from 10 to 25 per cent The frequency of such temporary icterus is not included in the data shown in Table IX of Part I the latter deals with persistent forms which develop either on the basis of definitive organic obstruction of the common duct or from metabolic disease with liver injury Transient jaundice was recorded in only about 8 per cent of our cases as compared with over 22 per cent of persistent icterus This temporary jaundice is usually accounted for on the basis of compression of the common bile duct by the edematous head of the pancreas

Gastrointestinal hemorrhage is occasionally a presenting symptom it is indicated by either bloody vomitus or bloody diarrhea

sudden death When such severe shock develops within the : 24 hours it is almost always a sign of massive hemorrhage › the pancreas with extension into the duodenum and retro :toneal tissues or necrosis of the pancreas death usually fol s promptly On the other hand the large majority of patients not lapse into shock unless loss of blood volume dehydration uncontrolled pain cause a fall in blood pressure several days r the onset of the disease Late shock may also result follow the delayed erosion of a vessel by enzymatic digestion

In the present series sudden severe shock with death follow promptly occurred in only six cases (4 per cent) moderately re shock developing several days after onset in 41 cases (25 cent) and mild shock in 53 cases (32 per cent) the remain cases were of such a mild nature that signs of shock were :r observed By comparison Paxton and Payne found severe k in 36 patients (11 7 per cent) moderate shock in 19 (6 2 :ent) and no signs of shock in 237 patients

'atients in severe shock often exhibit a peculiar ashy cyanosis ie extremities and face with pallor about the lips marked itension a rapid weak pulse and semicoma these signs are diagnostic of acute pancreatitis in the absence of other clini 'eatures of the disease Patients who develop such severe k rarely survive more than a few hours and unless the serum 'ase is elevated the diagnosis may be made only at autopsy he other hand subclinical shock as suggested by thirst pal 'estlessness and moderate fall in blood volume is present in of the moderately severe cases Elliott found a significant :t in blood volume in 71 per cent of severe cases and 12 5 :ent of patients with mild pancreatitis Defects appeared to ige 1500 ml and may appear in the first 24 hours of illness iugh the blood pressure may remain near normal and the : does not become exceedingly fast impending collapse may :tected by signs of dehydration

hus early severe shock may be attributed to massive hemor : or necrosis while milder degrees of shock gradual in ap ince may be due to depletion of blood volume by lesser de of hemorrhage by loss of fluid through persistent vomiting

Abdominal findings are of particular importance in an attack of acute pancreatitis Usually there is tenderness on palpation in a general area corresponding to the site of the primary pain Tenderness in the left flank or the lumbar area may accompany lesions in the tail of the pancreas or with irritation in the lesser peritoneal cavity Spasm of the abdominal muscles may be absent in mild cases and this may be helpful in a differential diagnosis although voluntary muscle guarding commonly occurs Peristalsis is usually normal or slightly hyperactive early and the abdomen is not distended with fluid or gas at this stage Diarrheal stools early in the disease is an indication of a reflex irritation of the colon prior to the onset of paralytic ileus Thus the overall absence of striking abdominal findings may distinguish acute pancreatitis in its early stages from other upper abdominal emergencies

With subsequent progression of the disease abdominal signs of greater significance may develop Epigastric tenderness becomes unequivocal and is associated with well defined muscle spasm in the upper abdomen this is due to a chemical peritonitis and reflex paralysis of the bowel The ileus most prominent in the jejunum is manifested by tympanitic swelling of the upper abdomen by absent or scarcely audible peristalsis and by constipation X ray studies at this time will give further evidence of ileus (Figures 50 51 52) Abdominal percussion may reveal shifting dullness in the flanks due to a generalized effusion and peritoneal tap may yield prune juice fluid which results from hemolysis Increased dullness and tenderness in the flanks when found may indicate the presence of clotted blood in these areas which does not move about in the peritoneal cavity An effusion within the lesser peritoneal cavity is almost impossible to detect in its early stages by physical examination but may be noted by its indirect effect on neighboring organs such as displacement of the stomach upward and forward elevation of the left diaphragm and pleural effusion at the base of the left lung If during the first week or two a tender mass becomes palpable in the epigastrium it is an indication that the foramen of Winslow may have become sealed off by inflammatory exudate within the lesser peri

most often due to acute ulcerations of the stomach duodenum or colon Such evidence of hemorrhage was found in twenty cases in the present series (12 per cent) and in 14 per cent in the study of Healey *et al* Paxton and Payne found bloody diarrhea in 4 5 per cent of their cases and hematemesis in 3 1 per cent Its importance derives primarily from the fact that it may constitute a misleading symptom The association of chronic gastric or duodenal ulcers and acute pancreatitis has been discussed in Part I, and such lesions may also present with symptoms of gastrointestinal hemorrhage

Diarrhea with or without blood was a presenting symptom in 7 per cent of the cases reported by Paxton and Payne and in 12 per cent in the present series Paxton and Payne attribute this symptom to the initial increase in peristaltic movements produced by peritoneal irritation to irritation of the autonomic nerve supply to the intestine and possibly to the absence of pancreatic enzymes in the intestines However most observers have found constipation a much more frequent symptom than diarrhea

Tetany occurs as a result of hypocalcemia and is usually observed after the first few days of illness While Edmondson and Berne have found some degree of hypocalcemia in 70 per cent of their cases only about 5 per cent developed clinical tetany There was no relation between the degree of depression of serum calcium and the development of symptoms of tetany

b) *Physical Findings Chest findings* were present in about one third of cases in the present series and this is in agreement with the frequency of such findings by Bockus *et al* The commonest finding is the presence of rales and occasionally a friction rub may also be heard In most instances such findings may simply represent a pneumonia sometimes with pleuritis or the development of pulmonary edema However the finding of elevation of the diaphragm and a pleural effusion at the base of the left lung may have more direct meaning It may constitute a physical expression of fluid in the lesser peritoneal cavity which may force the left diaphragm upward and also produce an irritation of it The pleural fluid in such an event may show a significant amylase titer

As previously noted ecchymoses about the umbilicus as described by Cullen and by Hofstatter or hemorrhage in the flanks as described by Turner may appear and represent blood extravasated into the retroperitoneal tissues from a marked hemorrhage of the pancreas However these signs are only occasionally observed and their usefulness in establishing a diagnosis is further diminished by their relatively late appearance in the illness usually between the third and tenth days Other skin manifestations have been described by Sigmund and Shelley Morbilliform lesions of the skin have been shown to exist over areas of subcutaneous fat necrosis Davis has observed cyanotic areas over the abdomen with petechial patches and some mottling of the skin of the limbs Sigmund and Shelley have also observed livido reticularis in a patient with acute pancreatitis characterized by an extensive area of cyanotic marble like reticulated discoloration over the abdominal wall and credit Walzel with having first described this manifestation on the abdomen chest and thighs Many of these lesions may represent an expression of the effects of circulating trypsin on subcutaneous vessels although such a mechanism has not been proved

c) ***Laboratory Findings*** The alterations in chemical and enzyme content of body fluids as described in Part II constitute the basis for the laboratory diagnosis of acute pancreatitis In many cases a definitive diagnosis rests in the final analysis on the demonstration of elevated enzyme levels in the blood and/or urine As has been pointed out the most widely used test in this regard has been the determination of amylase titers and the next most common has been serum lipase Blood tryptic levels have been studied only meagerly because of the difficulty in overcoming antitryptic substances present in the blood Elman has recently questioned the specificity of the serum amylase test for acute pancreatitis and elevated serum amylase values have been reported in perforated duodenal ulcers (Musgrove) acute cholecystitis (Wilson and Seabrook) renal insufficiency (Meroney *et al*) cerebral trauma (Smolik *et al*) and ectopic pregnancy (Kelley) As has been pointed out in Parts II and V even the administration of opiates can sometimes bring about significantly increased amylase levels (Gross *et al* Wapshaw Pfeffer *et al*)

toneal cavity and the trapped fluid has distended it Or it may be an indication of the formation of an abscess or pseudocyst



FIGURE 50 A hairpin loop of small intestine is seen in the upper left quadrant (arrows) (From Grollman A I Goodman S and Fine A Localized paralytic ileus An early roentgen sign in acute pancreatitis *Surg Gynec and Obst* 91 65 1950)

FIGURE 51 A flat plate made of the abdomen revealed an isolated gas distended loop in the mid abdomen (From Grollman A I Goodman S and Fine A Localized paralytic ileus An early roentgen sign in acute pancreatitis *Surg Gynec and Obst* 91 65 1950)

FIGURE 52 The solitary loop presents the typical herring bone appearance of small bowel (From Grollman A I Goodman S and Fine A Localized paralytic ileus An early roentgen sign in acute pancreatitis *Surg Gynec and Obst* 91 65 1950)

the importance of blood volume determinations for the recognition of incipient shock so that antishock therapy may be instituted early For this purpose he has utilized the radioactive iodinated serum albumin method of Crispell *et al*

✓ d) *Electrocardiographic Findings* These have also been discussed in Part II In the study of Bockus *et al* about 70 per cent of the patients on whom tracings were available showed evidence of myocardial abnormality and/or an electrolyte imbalance Electrocardiographic studies may be of value when correlated with serum electrolyte data and when myocardial infarction can be definitely excluded In our own studies evidence of myocardial infarction old or recent was found in 62 cases (38 per cent) and this is simply a reflection of the frequency with which acute pancreatitis occurs in individuals with cardiovascular disease There were also several cases in which the electrocardiographic changes were attributed to electrolyte imbalance but correlative data on serum electrolytes were not available Reece and Burrows have stressed in particular transitory S T segment and T wave changes in acute pancreatitis (Figure 53)

e) *X ray Findings* Radiographs of the chest may assist in arriving at a diagnosis if they show an elevation of the diaphragm with associated hydrothorax as noted below

X ray findings in the abdomen are particularly significant if they reveal secondary ileus Bockus *et al* have suggested the following criteria for establishing this event (1) The presence of air in a few loops of small bowel adjacent to each other and in the absence of significant air in other small intestinal loops (2) Small amounts of air in the stomach and/or colon (3) A caliber of the air filled loops of at least 2 5-3 cm (4) A stiffened appearance of the gas filled loops and a space between the adjacent loops wider than normal These various x ray manifestations of a localized ileus in acute pancreatitis have been well illustrated by Grollman *et al* (Figures 50 51 52) If these signs of a localized ileus are present in the upper abdomen either in the midline or left side they are considered as suggestive of acute pancreatitis Changes in the duodenum when present add further confirmation In particular ileus must be distinguished from

Furthermore it has been our experience that in fulminating hemorrhagic pancreatitis it may not be possible to demonstrate a significantly elevated blood or urine amylase titer

As detailed in Part II the levels of amylase in urine and blood are determined by the access of the released enzymes to the vascular system of the pancreas and to the integrity of the latter In those instances in which pancreatitis is on the basis of a vascular occlusion or vascular rupture and the pancreatic circulation is seriously impaired it may be that the released enzymes are unable to gain access to the general circulation It is also possible that in fulminating disease the peak serum enzyme levels are reached so rapidly and the enzymes excreted in the urine with such rapidity that peak titers are missed As regards circulating enzyme levels it is also pertinent to mention that Probstein *et al* were unable to find a direct correlation between the level of serum amylase and the intensity of the pancreatic process

In our own studies we have empirically adopted a serum amylase level of 1000 Somogyi units as highly indicative of acute pancreatitis and levels between 200 and 1000 as suspicious and pointing to the necessity of excluding from a differential diagnosis the diseases mentioned above which may also give elevated serum amylase titers In general the latter give titers of less than 1000 as has been pointed out with regard to perforated duodenal ulcers in Part I Pfeffer *et al* have recently described a technique for obtaining peritoneal fluid by use of a polyethyelene catheter on which amylase determinations may be carried out They regard hemorrhagic peritoneal fluid with a high amylase value (above 7000) as pathognomonic for acute hemorrhagic pancreatitis and their data show that perforated gastroduodenal ulcers may yields titers as high as 4820 units

Serum electrolyte changes have also been detailed in Part II and in this regard it is well to re emphasize the importance of a fall in serum calcium level and its relation to the development of tetany and the alterations in serum potassium and their relation to electrocardiographic changes

While not directly related to laboratory findings which may assist in the diagnosis of acute pancreatitis Elliott has stressed

to suggest pancreatic disease and can also establish the presence of pancreatic lithiasis It may also have value if when taken in an upright position presence or absence of a perforated ulcer can be determined on the basis of whether or not air is present under the diaphragm

f) *Clinical Course* Acute pancreatitis in its early stages *cannot be clinically differentiated according to pathologic types* as outlined in Part III but as the disease progresses certain features may appear which may make such a differentiation possible

1 *Acute edematous pancreatitis* if uncomplicated will typically run its course in two to three days after the onset of illness and be followed by prompt recovery Pain disappears appetite returns and soreness gradually leaves the epigastrium Within a week or less *the patient is sufficiently well to resume a normal* life In moderately severe attacks of this type the course rarely lasts beyond two weeks Transient jaundice is more likely to appear with acute edema of the head of the pancreas but fat necrosis even though widespread causes few if any symptoms

Acute necrotizing pancreatitis may at first appear deceivingly mild particularly *if progression of the disease is through a stage* of acute edematous pancreatitis If the patient fails to improve after several days and signs of intra abdominal inflammation persist or become intensified then it is likely that parenchymatous necrosis is taking place In fatal cases death usually occurs before the fourth day *but at times may be delayed for two to three* weeks until precipitated by secondary infection or pneumonia Glycosuria and hyperglycemia may occur in the course of severe pancreatic necrosis and disappear as recovery takes place this is the transient hyperglycemia previously discussed

Acute suppurative pancreatitis may develop as a result of secondary *infection following on the preceding forms of the dis*ease and will thus as a rule become manifest during the second or third week In other instances it may result from a primary bacterial invasion of the gland as with metastatic abscess formation septic embolization or as a suppuration extending directly from a neighboring *focus Such patients become extremely toxic* with high fever and the manifestations of a generalized infection

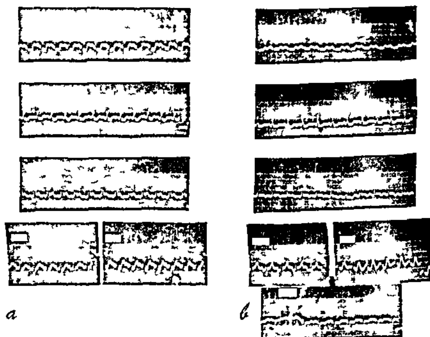


FIGURE 53 a) Electrocardiogram taken in a case of acute pancreatitis four hours after onset of pain showing depression of ST_1 and ST segments and elevation of the ST segment

b) The second day of the illness showing minimal ST segment changes Changes suggestive of left ventricular hypertrophy appear in both tracings (From Reeve C D and Burrows J B Acute diseases of the pancreas *Texas State J Med* 46 826 1950)

aerophagia in which the air is distributed uniformly throughout the entire gastrointestinal tract or is scattered in the stomach multiple loops of small bowel and several portions of the colon furthermore the loops of small bowel are not dilated

Cholecystograms may prove misleading While gallstones occur more frequently in cases of pancreatitis than in the general population the difference is not sufficiently great to be useful in a differential diagnosis Nor does the presence of calculi in the gallbladder particularly if jaundice is absent assist in establishing a common channel etiology which might indicate an attack of acute pancreatitis

A flat plate of the abdomen may on occasion prove valuable It can reveal displacement of organs in such an arrangement as

is usually in the right upper quadrant and may radiate around the back to the tip of one or both scapulae In acute gallbladder disease deep respiration may be painful and pressure over the right upper quadrant may produce excruciating pain on deep respiration Palpation of an enlarged gallbladder may also aid in a differential diagnosis and x ray studies may reveal the presence of stones in the gallbladder region Fever and chills tend to indicate cholecystitis but are not characteristic of acute pancreatitis

Perforated peptic ulcer A free perforation of a peptic ulcer may more nearly simulate acute pancreatitis than perhaps any other acute upper abdominal condition Furthermore as pointed out above the serum amylase may be elevated in this condition as well as with posterior ulcers which penetrate into the pancreas and produce pancreatitis (Probstein *et al*) In perforation of a peptic ulcer there is a more generalized abdominal rigidity than in acute pancreatitis and in many cases the entire abdomen becomes board like With perforated ulcer the patient usually lies quietly in bed whereas with acute pancreatitis he is commonly restless Usually in a perforated peptic ulcer there is a history of dyspepsia relieved by food or alkali although occasionally the perforation is the patient s first intimation of this disease Again roentgenograms may prove helpful particularly if a pneumoperitoneum can be demonstrated

Acute intestinal obstruction If this occurs in the upper abdomen it may particularly closely resemble acute pancreatitis Severe intermittent colicky pain of a cramp like nature is a most important symptom of such obstruction and generalized distention of the abdomen may also help in a differentiation from acute pancreatitis Epigastric muscle spasm and rigidity found in pancreatitis are not particularly pathognomonic of acute intestinal obstruction The vomiting of fecal material is indicative of a high intestinal obstruction The presence of visible peristalsis on the abdominal wall accompanied by audible sounds coincident with the onset of crampy pain suggests acute intestinal obstruction In the case of a mechanical bowel obstruction the peristaltic note is usually high pitched with evidence of a metallic sound

which may completely mask the symptoms of pancreatitis As a secondary event suppuration may occasionally begin a day or two following the onset of the disease but is more often first detected after five to seven days or more Unless a febrile episode occurs in the course of convalescence no clearcut signs mark the onset of suppuration which can be identified mainly by the abnormal rise in fever and increased leucocytosis

The hemorrhagic forms of pancreatitis if sufficiently severe will reveal a significant state of shock and abdominal findings as detailed above They may be present at the outset if the precipitating factor is a vascular rupture as in pancreatic apoplexy " On the other hand these symptoms may develop at any time in the course of the disease if progression of the pathologic lesion involves enzymatic digestion of vessels which are sufficiently large to cause extensive hemorrhage

g) ***Differential Diagnosis*** Differential diagnosis becomes important in view of several considerations As has been pointed out in Part V the basic therapy for bouts of acute pancreatitis is nonsurgical but erroneous diagnosis may lead to the neglect of a disease requiring immediate surgical intervention On the other hand an erroneous diagnosis leading to an operative procedure when in fact the disease is acute pancreatitis might also be injurious to the patient Time is a particularly important factor for many surgical lesions so that rapid accurate diagnosis is essential Furthermore pancreatitis may simulate cardiovascular disease and vice versa and here too erroneous diagnosis and erroneous therapy may prove critical Fortunately in many instances the determination of serum enzyme levels particularly amylase may serve to point up the correct diagnosis However as pointed out below this is not invariably the case and other diagnostic procedures may be important The following are the important specific diseases which must be differentiated from acute pancreatitis

Acute cholecystitis Frequently the pain of acute pancreatitis is indistinguishable from that of acute cholecystitis In the former however it is usually confined to the midline in the epigastrium or to the left upper quadrant while pain in acute cholecystitis

is usually in the right upper quadrant and may radiate around the back to the tip of one or both scapulae In acute gallbladder disease deep respiration may be painful and pressure over the *right upper quadrant may produce excruciating pain on deep* respiration Palpation of an enlarged gallbladder may also aid in a differential diagnosis and x ray studies may reveal the presence of stones in the gallbladder region Fever and chills tend to indicate cholecystitis, but are not characteristic of acute pancreatitis

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accompanied by peristaltic rushes and frequent succussion splashes On the other hand the paralytic ileus of acute pancreatitis is confined to the upper abdomen and is characterized by epigastric distention and hypo active peristalsis in that region Again roentgenography is of considerable assistance If the obstruction is mechanical in nature flat and upright abdominal films can be expected to demonstrate the presence of multiple fluid levels in the small bowel Furthermore the presence of a hernia abdominal scar from a previous operation or an abdominal mass may aid in the differential diagnosis

Acute appendicitis In most cases a differential diagnosis hardly presents a problem However when the appendix is retrocecal in position and also very long so that the body and tip are not too far removed from the gallbladder region acute inflammatory disease of the appendix may simulate the early stages of acute pancreatitis The pain is confined more to the right upper quadrant and the right side than to the epigastrium and the left upper quadrant Prostration as in acute pancreatitis is not particularly a sign of acute appendicitis In one of our cases acute pancreatitis followed rupture of an acute appendicitis and while signs shifted from those indicative of a right lower quadrant lesion to those of a generalized peritonitis the complication of acute pancreatitis was completely masked by the latter

Acute generalized peritonitis As has been pointed out this may completely mask the presence of acute pancreatitis when the two conditions occur together A history of an associated illness or abdominal lesion may point to a specific cause of the peritonitis not related to pancreatic disease Moreover the onset of acute pancreatitis if it precedes the peritonitis is usually more abrupt than the latter The presence of muscle spasm and tenderness over the entire abdominal wall is more suggestive of a generalized peritoneal inflammatory process than that usually seen in acute pancreatitis Diffuse distention associated with paralytic ileus is also a finding in favor of generalized peritonitis

Biliary colic and common duct stone Biliary colic of extreme degree may simulate acute pancreatitis The origin of pain in the former is apparently associated with such factors as spasm or

contraction of the gallbladder and distention of the cystic duct is usually associated with acute cholecystitis and obstruction or with inflammation associated with the presence of a stone The pain is usually paroxysmal and localized to the right upper quadrant of the abdomen The history and nature of onset of acute cholecystic obstruction in conjunction with physical findings should make a clearcut differentiation possible The presence of jaundice fever and chills would also strongly point to biliary colic

Splenic rupture Hinshaw and Murray have recently reported two cases of splenic rupture simulating pancreatitis Pain distribution was similar to that found in acute pancreatitis with nausea vomiting and in one case shock Serum amylase was moderately elevated and in one instance urinary amylase was 2720 units in one case This condition may on occasion be clinically indistinguishable from acute pancreatitis and the authors conclude that surgical intervention should not be delayed because laboratory evidence suggests pancreatitis if any suspicion of splenic hemorrhage remains

Renal colic In particular a stone in the left ureter may create difficulty in differential diagnosis The pain of renal colic is knife like and usually radiates toward the thigh or genitalia When the stone enters the ureter the pain may be so excruciating as to produce nausea and vomiting with spasm of the abdominal wall and even collapse of the patient The finding of hematuria is a critical point in establishing the correct diagnosis

Pneumonia This disease may raise problems in differential diagnosis, particularly if there is an associated diaphragmatic pleuritis The rapid onset of pain in the chest cough cyanosis dyspnea fever and leukocytosis all point to a pneumonitis as do the increases in respiratory and pulse rates and labored respirations When in the early stages of pneumonia there is pain or discomfort referred to the upper abdomen the differential diagnosis may be difficult Roentgenograms of the chest may not always help to differentiate these two conditions and the differentiation may rest with a thorough examination of the chest along with serum amylase determinations and a history of cough and rusty sputum

Tabetic crisis This event is rapidly becoming extinct It may however be accompanied by extreme abdominal pain nausea vomiting and a mild degree of shock Positive serology the finding of Argyll Robertson pupils and neurological examination all serve to make an adequate differentiation between the two diseases

Acute coronary occlusion This disease notoriously resembles such important surgical conditions of the abdomen as gallstone colic acute appendicitis perforated peptic ulcer acute intestinal obstruction and acute pancreatitis The presence of dyspnea and the radiation of pain to the sternum or arms may be helpful in differentiating acute coronary disease Positive electrocardiograms may in some instances yield the only clearcut distinction although this may now be supported by such laboratory tests as elevated transaminase and lactic dehydrogenase levels

Dissecting aneurysm of the aorta Differential diagnosis may be particularly difficult when the dissecting aneurysm occurs in the upper abdominal aorta since this event is associated with a severe degree of pain in the upper abdomen and a state of shock similar to that seen in acute hemorrhagic pancreatitis Usually in a dissecting aneurysm when perforation through the adventitia does not occur the blood pressure will remain elevated Another helpful sign is obtained when there is occlusion of branches of the aorta supplying the kidneys or the lower extremities If the aneurysm is progressive femoral pulsations may be impaired and the blood pressure in the legs may be reduced to a level equal to or lower than that in the arms The absence of electrocardiographic changes may serve to rule out acute coronary occlusion If the aneurysm ruptures into the peritoneal cavity there is associated marked abdominal rigidity shock and death similar to that found in pancreatic apoplexy

Mesenteric Thrombosis This event may sometimes present as an intestinal obstruction with a less acute onset and thus simulate pancreatitis However it may be associated with slight bloody diarrhea which is rare in acute pancreatitis Shock is more acute than in most cases of acute pancreatitis but may lead to an erroneous diagnosis In mesenteric thrombosis diffuse tenderness

and rigidity are common and x ray studies may show a large dilated loop of bowel representing the seat of infarction A history of cardiac disease is often an important clue

Miscellaneous Other diseases which may more superficially simulate pancreatitis are hemoperitoneum from a tubal abortion or ruptured graffian follicle pulmonary embolism and pulmonary infarction diaphragmatic hernia with incarceration early left sided herpes zoster angina pectoris acute arthritis of the thoracic spine acute porphyria acute lupus erythematosis traumatic rupture of the aorta and even more rarely the crisis associated with progressive hemachromatosis The areas of similarity generally consist of intensity and distribution of pain caused either by neurologic disease diaphragmatic irritation cardiac pain or pain associated with embolism and blood in the peritoneal cavity with symptoms of peritoneal irritation

Paxton and Payne have been able to consolidate these varied clinical manifestations of acute pancreatitis into the following five basic groups which express also the problems of differential diagnosis

1 Those patients whose symptoms fit the classical textbook description of acute pancreatic necrosis Shortly after the ingestion of a heavy meal or an excessive amount of alcohol an obese middle aged person experiences sudden onset of severe steady pain with associated nausea and persistent vomiting Cyanosis and shock soon become evident and the disease terminates fatally in a relatively short period of time These cases most closely resemble acute coronary occlusion

2 Those patients having signs and symptoms suggestive of acute cholecystitis The pain is less severe than in the first group and becomes localized to the right upper quadrant frequently radiating to the back and accompanied by less persistent nausea and vomiting There is often a history of similar previous episodes

3 In this category patients typically have symptoms resembling acute intestinal obstruction There is severe abdominal pain with nausea vomiting distention and obstipation

4 Patients in this group have symptoms suggesting peptic ulcer or alcoholic gastritis While some degree of epigastric pain and tenderness are present persistent nausea and vomiting are the most striking features

5 These patients typically enter the hospital several days after an acute attack of upper abdominal pain tenderness nausea and vomiting They have a tender palpable epigastric or right upper quadrant mass

6 A sixth category has been suggested by Cattell and Warren which would include a considerable number of patients with mild ill defined symptoms nonspecific in localization and detail They suggest that this is the most common variety of inflammation of the pancreas

Becker has also divided his series of 100 cases according to the five groups of Paxton and Payne Ten per cent of his cases were in the first group 26 per cent in the second 20 per cent in the third about 30 per cent in the fourth and 11 per cent in the fifth

Chapter 17

THE CLINICAL MANIFESTATIONS OF THE COMPLICATIONS AND SEQUELAE OF ACUTE PANCREATITIS

The complications and sequelae of inflammatory disease of the pancreas fall into two groups The first includes those secondary events which occur during an attack of acute pancreatitis with no antecedent history of similar disease or during an acute exacerbation of chronic relapsing (recurrent) pancreatitis Certain of these have already been discussed in the previous section among them are such events as pleural effusion ascites the formation of hematomata extra abdominal fat necrosis and fat embolism Other lesions which fall into this group are abscesses within the pancreas or the abdominal cavity and pseudocyst The second group consists of events which develop later and includes chronic relapsing (recurrent) pancreatitis diabetes intestinal obstruction on a mechanical basis due to the development of adhesions the formation of fistulae and pylephlebitis with thrombosis of the splenic and/or portal vein

a) *Abscess Formation* True abscess formation as distinguished from areas of liquefaction necrosis were found in 17 cases (10 4 per cent) in the present series Fourteen of these were in patients who gave no antecedent history of attacks of pancreatitis while the remaining three were in patients with known previous acute bouts Whenever a temperature above 101 F is encountered this complication should become suspect Hardy and Bowlin point out that the alert and persistent examiner will occasionally be rewarded by palpating a mass in the left flank region which appears to be the most common site of abscess formation As pointed out previously corroboration of this complication may also be obtained by careful examination for displacement of organs x ray examination of the abdomen is particularly useful for this purpose Laboratory tests are gener

ally unrevealing although a leucocytosis in association with a febrile course and a palpable mass can be considered significant

b) ***Pseudocyst Formation*** This complication was present in only one of the cases in the present autopsy series although Probstein has reported an incidence of 1 4 per cent of 370 clinical cases at this hospital As has been pointed out a pseudocyst may develop during an acute attack particularly if trauma or extensive hemorrhage has occurred or it may occur after the initial attack or between attacks in cases with *recurrent disease* Most commonly pseudocyst is discovered three or four weeks after a severe bout of acute pancreatitis *Sinclair has stated that the preoperative* diagnosis requires above all that the clinician bear the possibility *in mind when confronted with a patient presenting atypical upper* abdominal complaints According to Judd *et al* and Adams and Nishijima *pain is the commonest presenting symptom it is* usually epigastric although sometimes it radiates to the back *The pain is constant dull and* aching in character *it may be* episodic and suggestive of a recurrent attack of pancreatitis or *associated disease of the biliary* tract

The symptoms arise for the most part as a result of pressure exerted by the pseudocyst on the stomach duodenum bile ducts or colon they are therefore so variable as to be in themselves of little diagnostic aid The most reliable single clinical feature is the presence of an upper abdominal mass as first pointed out by Korte The mass is characteristically deeply placed rounded and does not move on respiration it is usually slightly tender and may vary in size from time to time Occasionally a cyst arising from the tail of the pancreas may be surprisingly mobile In those cases in which a history of antecedent pancreatitis is not obtainable such signs as steatorrhea impaired glucose tolerance glycosuria or a non functioning gallbladder when present may serve as additional support for the diagnosis

If a pseudocyst develops during an attack of acute pancreatitis serum diastase values are often in excess of 1 000 Somogyi units but in those cases in which this lesion is discovered at other times titers are usually around 200 300 and are sometimes within normal limits By far the most valuable diagnostic tool is radio

graphy following a barium meal with particular importance being attached to the lateral view Depending upon the location of the cyst there will be distortion of adjacent viscera In Figures 54 and 55 are shown distortion of the posterior wall of the stomach by pressure from such a cyst as well as the return of the stomach to almost normal following therapy discussed in Part V In other cases there may be evidence of extrinsic pressure on the duode num widening of the duodenal loop and sometimes displacement of the duodenal jejunal angle

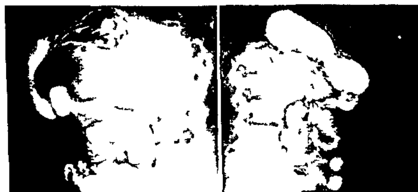


FIGURE 54 Lateral view showing distortion of the posterior wall of the stomach by pressure from a pseudocyst (From Probstein J G Pseudocyst of the pancreas Diagnosis and therapy *A M A Arch Surg* 69 425 1954)

FIGURE 55 Same case as in preceding figure two weeks later showing return of stomach to almost normal shape following cystogastrostomy (From Probstein J G Pseudocyst of the pancreas Diagnosis and therapy *A M A Arch Surg* 69 425 1954)

If the content of a pseudocyst is sterile there may be little or no systemic reaction but if bacteria become established abscess formation occurs and a febrile episode develops with a more or less concomitant leucocytosis The clinical manifestations thus become those of an abscess and with virulent infection the sub sequent course is stormy and frequently fatal

c) *Mechanical Small Bowel Obstruction* Hardy and Bowlin have pointed out that the most common site for such obstruc tion is of the duodenum or jejunum near the ligament of Treitz It may also occur at the level of the second portion of the duode

num Such obstruction may be due to extrinsic pressure caused by an abscess or pseudocyst or it may be the result of adhesions developing between the pancreas and adjacent bowel Clinical evidence of such intestinal obstruction may develop during an attack of acute pancreatitis or some time after the attack has subsided It is important that such mechanical obstruction be differentiated from the paralytic ileus which occurs during an acute attack since the former may require definitive surgical therapy Thus if symptoms of obstruction persist after the acute bout has subsided x ray examination of the gastrointestinal tract is in order for purposes of localizing the obstruction and determining its basic nature

d) *Persistent Biliary Obstruction with Jaundice* Persistent jaundice associated with pancreatitis may of course be due to a common duct stone but it may also be due to compression of the duct by fibrotic and calcareous changes resulting from recurrent attacks of acute pancreatitis It is often difficult even with biopsy to distinguish between the latter process and obstruction due to malignant disease of the head of the pancreas

The clinical signs and symptoms in this situation are typical of those of obstructive jaundice and need not be detailed here Its true nature may become apparent if a history of recurrent bouts of acute pancreatitis are elicited or if other evidence of deficiency of exocrine function of the pancreas is obtained Differentiation as to whether biliary tract obstruction is due to a calculus or compression by the hard head of the pancreas rests in the final analysis with x ray studies of the biliary pancreatico ductal systems

e) *Fistula Formation* A spontaneous fistulous communication between skin and pancreas apparently does not occur but such tracts may develop spontaneously following the adherence of a pancreatic abscess to small bowel On the other hand in the therapeutic marsupialization of a pseudocyst the fistulous opening may become stenosed this is usually accompanied by a febrile reaction and the infected pseudocyst forms an abscess The development of a spontaneous fistula between pancreas and small bowel is apparently very rare but such an event may serve

to drain an abscess spontaneously The fistulous tract would probably go undiscovered unless a gastrointestinal x ray study were performed since it would most likely be asymptomatic A spontaneous fistula may also develop between a pseudocyst and the pancreas when the former communicates with a major pancreatic duct Probably the most common event leading to fistula formation is that pointed out by Child and Donovan They state that a fistula almost inevitably develops following drainage of the site of extensive pancreatic injury and the same is true for drainage of an abscess or a localized collection of blood Frequently patience over a period of months is required to observe spontaneous closure but surgical closure is not required

f) ***Pylephlebitis*** Gambill mentions this lesion among the complications of chronic relapsing pancreatitis but does not elucidate further on its clinical or pathological manifestations Since the pancreas is drained by the splenic portal venous system septic venous emboli in suppurative pancreatitis conceivably occur Such an event was demonstrable at autopsy in two of our cases which showed abscesses of the pancreas and multiple abscesses of the liver While these patients ran a septic course there was nothing distinctive in their clinical manifestations which would distinguish this complication It should probably be considered in those cases of recurrent pancreatitis in which there is enlargement of the liver and spleen and evidence of sepsis needle biopsy of the liver might be considered as a means of determining a septic process in that organ which would further support the diagnosis of thrombophlebitis of the splenic and portal veins

g) ***Chronic Relapsing (Recurrent) Pancreatitis*** An initial attack of acute pancreatitis appears to render the pancreas susceptible to subsequent similar attacks and such recurrences probably constitute the most frequent sequel of the acute disease In part this is indicated by the frequency with which a history of previous episodes suggestive of acute pancreatitis can be obtained In reviewing the literature Roberts *et al* have concluded that in 40-75 per cent of patients such an antecedent history has been obtained In part it is also supported by other reports reviewed by Roberts *et al* which show that 50-75 per cent of patients experiencing acute necrosis of the pancreas will usually

have a history of some type of chronic upper abdominal distress preceding the onset of a clinically diagnosed bout of acute pancreatitis. Bockus *et al.* have concluded that alcoholics have a higher incidence of such recurrences and also that pancreatic calcification appears six times more frequently in alcoholics than in other groups with chronic relapsing pancreatitis. The tabulation below indicates the recurrence rate in certain selected reports as compared with the present series. Not only has the recurrence rate at this hospital been much lower than the general experience but the pathologic changes characteristic of recurrent disease have been found much less frequently.

Author	*Recurrence Rate*
Love	61 per cent
Elman	63 per cent
Fallis and Hun	53.8 per cent
Lewison	71 per cent
O'Brien and Thayer	74 per cent
Present series	13.5 per cent

While, as has been pointed out with respect to acute pancreatitis, there is either an equal distribution between the two sexes or a slight predominance of females in various reports, Gambill has reported that chronic relapsing pancreatitis occurs roughly 3 to 6 times as often in males as in females. The peak age incidence also is slightly different than in acute pancreatitis in that the recurrent disease is most common in the fourth and fifth decades, the average age at onset being approximately 39 years.

A carefully obtained history is particularly important with respect to this disease. In many instances a history of drug addiction and alcoholism may prove useful in evaluating the severity and duration of the disease. Gross and Comfort have emphasized the hereditary characteristic of certain cases and Klatskin and Gordon the familial nature of some associated with hyperlipemia.

Gambill has presented the most detailed account of the clinical manifestations of relapsing pancreatitis, in particular the nature and distribution of pain. He points out that an occasional patient seems to experience certain prodromal symptoms a few hours to a few days prior to the actual onset of pain. These often consist of anorexia or nausea, severe bloating or gaseous distention or

even unusual fatigability Pain can be relatively mild and only of a few hours duration involving almost any part of the abdomen However it is more commonly severe protracted for days and even up to two or three weeks and requiring much morphine Pain is often gradual in development and cessation It is commonly of a steady nature but there may be superimposed waves of exacerbation It has been variously described as cutting piercing colicky crampy and boring The attacks often become increasingly frequent severe and prolonged but occasionally diminish in frequency and intensity

The pain may appear in any part of the abdomen spreading down and around or through the trunk to involve the upper lumbar region of the back At times it may be confined to the right upper quadrant and the corresponding level of the back and thus be mistaken for gallstone colic However in pancreatitis such pain commonly lasts for days while in cholelithiasis it usually lasts for only a few hours Occasionally the pain may shift to the left antero inferior thoracic region Usually but not always pain is referred to the upper lumbar region of the back While during an attack pain may be felt in any part of the abdomen it is most characteristic when it shifts to or is primarily centered in the left upper part of the abdomen and the left lumbar region of the back

Nausea and vomiting may accompany the attack of pain sometimes affording some relief Retention vomiting may be due to duodenal obstruction often by compression from a pseudocyst Generalized abdominal distention due to gas is often encountered with inability to belch or pass flatus such patients sometimes describe a feeling that all gastro intestinal activity has ceased Occasional patients volunteer the statement that the passage of flatus is often followed by a cessation of pain The entire abdomen is often tender so that coughing sneezing deep inspiration or twisting motions of the abdomen are done with reluctance Such tenderness anorexia and weakness may persist for several days after the pain has ceased Marked obstipation and abdominal distention rather than diarrhea seem to be the rule during such an episode

Between such episodes patients may complain of a variety of symptoms such as heartburn gnawing epigastric distress which at times may mimic peptic ulcer flatulent dyspepsia and intolerance of fatty foods Alcoholics occasionally experience nausea vomiting and actual hematemesis presumably from an associated gastritis

In patients with advanced disease fatty voluminous foul smelling stools characteristic of steatorrhea are experienced Such patients often lose considerable weight and strength Weakness fatigability and melancholia are also common interval symptoms Symptoms of diabetes may also appear and these have been detailed separately

Physical examination may be completely negative between attacks of pain except for epigastric tenderness not specific for any disease During an acute exacerbation there is often diffuse abdominal tenderness of both the direct and rebound type usually greatest in the epigastrium Muscle guarding and spasm are present greatest also in the upper abdomen but not board like rigidity With the more severe attacks associated with fat necrosis in the mesentery the findings may simulate a generalized peritonitis with tenderness distention faint or absent peristaltic sounds *and even ascites Adynamic ileus may be evidenced by* absent peristaltic sounds distention of the stomach and bowel with gas and secretion and an inability to pass flatus Gastric retention may occur either as a result of such ileus or due to obstruction of the duodenum by the enlarged pancreas The appearance of audible gurgling in the abdomen and the passage of flatus are indications of the end of the attack

A tender mass representing an enlarged pancreas may be felt lying transversely in the epigastrium As the tenderness subsides one may occasionally be able to palpate a pancreatic pseudocyst

Patients may assume a variety of postures during an attack of pain Some lie quietly in bed reluctant to take a deep breath cough or turn over owing to abdominal tenderness Others assume a sitting posture with trunk flexed and forearms folded across the abdomen in order to exert pressure against it

Shock is relatively uncommon in relapsing pancreatitis except during a severe episode of hemorrhagic necrosis with which event there is a high mortality Although low grade to moderate fever may be present rigors and high fever are uncommon in the absence of a complication such as pancreatic abscess pyle phlebitis and multiple abscesses of the liver In some cases a low grade icterus may be observed usually due to compression of the common bile duct by the enlarged head of the pancreas Oc casionally an enlarged tender liver and spleen are palpated but these are not characteristic of the disease Ascites may develop whenever fat necrosis is extensive throughout the abdomen

A greater variety of laboratory tests are usually utilized in the recurrent disease than with a single attack of acute pancreatitis During an acute exacerbation the urine may show albumin casts and erythrocytes as well as a transient or persistent glycosuria Likewise hyperglycemia may be either transient or lasting Whenever glycosuria or an elevation of the fasting blood sugar level are encountered it is advisable to perform a glucose toler ance test after the attack has subsided in order to determine whether or not permanent diabetes is present

The blood urea may be elevated and the chlorides and CO_2 combining power altered if dehydration vomiting toxemia and shock have been part of the clinical picture Hyperlipemia may be present prior to an acute attack particularly if the case is one of familial hyperlipemia or it may occur as an effect of the disease

During the acute attack the concentration of serum amylase and lipase tend to be increased except in those cases in which the damage to the pancreas is so extensive as to destroy most of the acinar tissue Some investigators have resorted to the use of morphine mecholyl or urecholine to produce obstruction and cause a rise in amylase or lipase in those cases in which these tests are otherwise inconclusive in this way they attempt to distinguish between normal persons and those with subacute or chronic pancreatitis (Burke *et al*) While a rise usually can be elicited in an acute or subacute exacerbation in far advanced fibrosis of the pancreas the fasting enzyme values tend to be lower and the

rise less There may be a depression of the serum calcium level during an acute exacerbation as previously described

The serum bilirubin concentration may be increased during an acute seizure particularly if the process involves the head of the pancreas and causes compression of the common bile duct In some instances however there may be an associated suppurative process in the liver responsible for the hyperbilirubinemia Hypoproteinemia is common among patients with severe nutritional disturbances

The sedimentation rate is often an index of the course of an acute exacerbation It is accelerated during the acute phase and usually returns to normal between seizures A low grade hypochromic normocytic anemia is common among these patients Leukocytosis is not an important finding in recurrent pancreatitis although a moderate increase may occur during an acute phase

The appearance of voluminous greasy malodorous stools is an indication of steatorrhea which may be confirmed by chemical determination of the fat content of the stools The latter is usually feasible only between attacks The absence of enzymes responsible for such steatorrhea may be further confirmed by the secretin duodenal drainage test discussed in Part II



FIGURE 56 Flat plate of the abdomen showing a calcific mass to the right of the vertebral column (arrow) which proved to be a calculus occluding the duct of Wirsung

Roentgenograms of the abdomen are particularly valuable as a means of detecting calcific deposits in the region of the pancreas (Figure 56) They are sometimes discovered in x rays taken for other purposes such as those of the lumbar portion of the spinal column in excretory urograms in cholecystograms or in the course of a gastrointestinal series The calcific deposits may be finely punctate or conglomerate masses sometimes both are present They may be distributed evenly or irregularly throughout the region of the pancreas Multiple calculi may outline the course of the duct of Wirsung

Cholecystograms taken during or soon after the acute phase of the disease may reveal a poorly functioning or nonfunctioning gallbladder but this examination should be repeated after complete recovery since in many cases such examination then discloses normal function They may be explained on the basis of acute or subacute cholecystitis developing as a result of the reflux of pancreatic juice into the biliary tree as described in Part II

Gastrointestinal x rays may reveal other abnormalities of a secondary nature The enlarged inflamed pancreas may compress the stomach or become adherent to it likewise there may be compression and obstruction of the duodenum with resulting gastric dilatation Inflammatory adhesions may also produce a deformity simulating a duodenal ulcer In an occasional patient such studies may also reveal hypermotility of the small intestine or a pattern suggestive of a deficiency state

Thus chronic relapsing (recurrent) pancreatitis is characterized by recurrent attacks of abdominal pain with associated manifestations of disturbed function of the exocrine and sometimes the endocrine portions of the pancreas as well as various disturbances of the biliary and/or gastrointestinal tracts On the other hand there are other cases which although they appear to be of a similar basic nature as judged by laboratory and x ray findings nevertheless do not present this typical clinical picture Gross and Comfort have described cases in which the pain may be short and mild or even absent in contrast to the severe prolonged painful seizures which constitute the hallmark of the typical cases In the absence of pain the diagnosis is seldom

suspected except in those rare instances in which palpation of the pancreas at surgical exploration for other causes reveals this disease, when roentgenogram of the upper abdomen by chance discloses calcification or steatorrheal diarrhea takes the patient to the physician In three cases in our own autopsy experience there were no clinical symptoms of this disease and calculi in the pancreatic ducts were discovered only as an incidental ne cropsy finding Similarly Gambill and Pugh have reported that in four of their 29 cases of pancreatic calcification the patients had neither pain steatorrhea nor diabetes and Mayo also found one such case in a group of nine with pancreatic lithiasis in an autopsy study Occasionally such cases free of pain present with painless jaundice of obstructive type Painless pancreatitis un questionably occurs and has been reported by Maimon *et al* Vachon and by Bartholomew and Comfort many of the cases in the present series recorded as incidental discoveries at autopsy properly belong in the same category Bartholomew and Comfort have stressed the discovery of such symptomless cases in patients whose chief complaints at the time of initial examination were related to diabetes Other patients present with only steatorrheal diarrhea as a complaint and they are often studied from the standpoint of primary pancreatic atrophy carcinoma of the pan creas calculus blocking the duct of Wirsung, Whipple s disease non tropical sprue and the steatorrheal diarrhea complicating diabetes mellitus with neuropathy before the true nature of the underlying disease is discovered

At the other end of the spectrum we have encountered cases in which there was continuous low grade abdominal pain for pe riods of months or even years without remission and without significant fluctuation in intensity of symptoms except as accom plished by therapy As a rule such patients are alcoholics At the present time at least no etiologic or pathologic differences have been found to account for such wide variations in the sever ity of clinical symptoms

h) *Diabetes* As has been pointed out previously, and re cently emphasized by *Bell* hyperglycemia and glycosuria may be demonstrated during any severe attack of pancreatitis but if

the patient survives the signs of diabetes usually subside gradually although an impaired glucose tolerance may be demonstrated for several months The reports in the literature as compiled by Bell, show a frequency of diabetes following pancreatitis ranging from 2 to 30 per cent, depending upon the type of pancreatitis and the author s definition of diabetes *In general it is agreed* that acute pancreatitis may be followed by a diabetes of short *duration but rarely by a prolonged diabetes In Shumacker s* large series of cases of acute pancreatitis permanent diabetes was found in less than 2 per cent

Sprague credits Cawley with recording one of the earliest descriptions of a case of chronic pancreatitis with pancreatic calculi Cawley described the case of a man aged thirty four years strong healthy and corpulent accustomed to free living and *strong corporal exertions in the pursuit of country amusements"* who in December 1787 was seized with diabetes He gradually became emaciated and debilitated and his urine was found to be sweet and to contain a substance which was fermentable with yeast After treatment with a variety of medicines the usual consequence of inefficacy and despair the patient died An autopsy was performed "The pancreas was full of calculi which were firmly impacted in its substance They were of various sizes not exceeding that of a pea white and made up of a number of lesser ones which made their surface rough, like mulberry stones and in all respects they appeared analagous to the calculi which we sometimes meet within the salivary ducts The right extremity *of the pancreas was very hard and appeared to be* scirrhous

While Cawley thought that the condition observed in the pancreas was a complication rather than the cause of the diabetes it is now generally recognized that permanent diabetes is especially prone to develop as a complication in chronic recurrent pancreatitis and that this complication occurs more often when there is associated pancreatic lithiasis In compiling data from eleven reports Bell found an incidence of diabetes in 14 per cent of 253 cases of chronic pancreatitis without lithiasis as compared with the combined data from thirteen reports containing 255 cases of chronic pancreatitis with lithiasis in which the in

cidence of diabetes was 45 per cent From these and his own data Bell concluded that permanent diabetes rarely follows acute pancreatitis but that it frequently follows recurrent pancreatitis In the absence of calcification diabetes is found in about 14 per cent but when lithiasis is present in addition the incidence rises to 45 per cent

The sequence is however not quite as clearcut as the fore going figures might lead one to believe Thus in the series of 24 cases of diabetes and chronic recurrent pancreatitis reported by Sprague 15 had symptoms of pancreatitis preceding the discovery of diabetes by more than five years but there were five cases in which less than a year elapsed between the onset of symptoms of pancreatitis and the discovery of diabetes and in four others pancreatitis preceded the diabetes by less than five years and more than one In certain instances a familial history of diabetes may further cast doubt on this relationship Nevertheless it ap pears that in most severe cases there is sufficient destruction of islet tissue to create a permanent diabetes and Duncan *et al* have recently reported a case of recurrent pancreatitis and diabetes in which there was progression to retinopathy and nephropathy of diabetes with death due to these complications

There are apparently no sharp clinical signs which herald the onset of permanent diabetes The latter is usually discovered be cause of the high index of suspicion for this complication created by the numerous reports showing the association with recurrent pancreatitis Once glycosuria and hyperglycemia have been de tected glucose tolerance studies should be instituted periodically to chart the course of the disease and to determine the necessity of continuing therapy

Sprague further points out that the course of the diabetes is characterized in general by a tendency to be transient or mild in the beginning and to become permanent and increasingly severe as more and more of the pancreas is destroyed with the passage of time and with the occurrence of exacerbations Once perma nant diabetes is established it exhibits fluctuations in severity corresponding to exacerbations and remissions of the inflamma tory process in the pancreas He suggests that the flare ups of diabetes may be due not solely to diminished production of in

sulin by the pancreas during acute attacks but also to aggravation of the disease such as may occur in any case of diabetes with almost any intercurrent illness particularly if the latter is associated with pain or a febrile course

SUMMARY

The clinical manifestations of both the acute and recurrent forms of pancreatitis thus mirror the pathologic physiology and anatomy as presented in Parts II and III In both the effects on various nerves may be related to the intensity and distribution of the pain as well as to the development of paralytic ileus in the acute disease this is the result of pressure by edema and the irritant effects of inflammatory exudate while in the recurrent forms it is the result of acute and chronic inflammation and compression by scar tissue Nausea and vomiting are probably due to effects on nerves as well as direct irritant effects of inflammation and distention is the result in part of the development of ileus and in part the accumulation of exudate in the abdominal cavity Shock is due to multiple factors the most important of which are hemorrhage resulting from vascular digestion or degenerative vascular disease and loss of fluid through exudation and vomiting these are reflected in blood volume losses Fever and toxemia are signs of sepsis usually indicating either secondary abscess formation or the development of pancreatitis on an infectious basis The concentration of calcium in foci of fat necrosis is mirrored in a depression of blood calcium and the development of signs and symptoms of tetany Pleural exudate high in amylase is due to irritation of the diaphragm by abdominal inflammatory exudate or dissemination of fat necrosis to the pleural cavity Secondary effects on the heart may be the result of electrolyte imbalance particularly potassium or again the dissemination of fat necrosis to the epi and myocardium *Perhaps most difficult to* account for from the standpoint of clinical signs and symptoms are the effects of increased circulating enzyme levels particularly trypsin While such events may account in part at least for toxemia and shock the latter could occur in any event as a result of tryptic digestion of tissue and of fluid and blood loss

The occurrence of palpable abdominal masses have been shown to represent the development of abscess or pseudocyst

or the distention of a paralyzed segment of intestine Icterus can be accounted for on the basis of either temporary obstruction of the common bile duct by edema of the head of the pancreas or more permanent compression by a hard fibrotic sometimes calcified lesion of this portion of the organ

In the process of healing and with recurrence of acute bouts followed again by additional scar formation the exocrine and endocrine elements of the pancreas are destroyed The deficiency states thus produced are expressed in symptoms due to a lack of digestive enzymes normally supplied by the pancreas (steatorrhea azotorrhea etc) and by diabetes Chronic inflammatory changes about nerves are probably sometimes responsible for consistent low grade pain even without remission On the other hand there are certain cases in which pain is an insignificant symptom and pancreatic ductal lithiasis is only incidentally discovered As pointed out in Part II such cases should be particularly studied from the standpoint of subclinical parathyroid disease a consideration which appears to have not yet attained wide recognition

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PART V

THERAPEUTIC MEASURES IN PANCREATITIS

THERAPEUTIC CONSIDERATIONS IN PANCREATITIS

As Siler and Wulsin have pointed out acute pancreatitis was considered a surgical emergency for many years Operative procedures included multiple incisions into the capsule of the pancreas with drainage drainage of some portion of the extrahepatic biliary tract (cholecystostomy or choledochostomy) or drainage through the foramen of Winslow On rare occasions some surgeons have advocated drainage of both the pancreas and the extrahepatic biliary tract

Largely through the influence of reports by Elman Probstein *et al* Abell Cole, Morton Popper and more recently Machella Dreiling and Richman Ivy and Gibbs and Berk a more conservative approach to the treatment of the various forms of acute pancreatitis has gradually evolved However there are still a few who continue to advise surgical intervention despite the fact that surgical drainage of the pancreas or of the bile ducts during the acute stage of the disease has carried a mortality of about 40-50 per cent whereas with conservative therapy the mortality has been significantly reduced

On the other hand surgical intervention may be required for certain of the immediate complications and later sequelae Some of these such as abscess collection of blood and/or pancreatic fluid and pseudocyst formation may constitute relatively early complications requiring operative intervention Late sequelae such as pancreatic lithiasis associated gastrointestinal or biliary tract lesions and instances of intractable pain in chronic relapsing (recurrent) pancreatitis may also require surgical attention

Chapter 18

THE TREATMENT OF ACUTE PANCREATITIS

Because it may not be possible to differentiate at the outset between an attack of acute edematous (transient) pancreatitis and the more severe forms, conservative measures are generally utilized at least until there is some indication of the general behavior of the disease usually within the first four or six days Such medical management of acute pancreatitis is directed toward the following problems

a Relief of pain
b Control of spasm of sphincter of Oddi
c Treatment of shock
d Replacement of fluids and electrolytes
e Temporary suppression of pancreatic secretion
f Prevention and control of distention
g Prevention of suppuration
h Management of disturbances of carbohydrate metabolism

a) ***Relief of Pain*** Control of the intense unrelenting pain of acute pancreatitis is important not only for the immediate comfort of the patient but also as Gold *et al* have observed because severe pain has a marked vasoconstricting effect When important structures are involved as for example the heart such an ischemic phenomenon may prove fatal Jones has pointed out that there are a number and diversity of such agents among the more commonly used of which are morphine sulfate (10 15 mg) dihydromorphinone hydrochloride (Dilaudid 2 4 mg) meperidine hydrochloride (Demerol 100 150 mg) Codeine 65 mg and the intravenous administration of a 0 1 per cent solution of procaine hydrochloride

These agents relieve pain by their central action While morphine and its derivatives possess the most powerful analgesic and sedative action it has been pointed out by Wapshaw and others

that they increase the tension of the smooth muscle of both the digestive tract and the pancreatico-biliary ductal system including the sphincter of Oddi Their use is also limited by the possibility of producing addiction in the event the disease is of a recurrent nature While Demerol is generally considered the drug of choice for the pain of pancreatitis it also increases tension of the gastrointestinal muscle and of the sphincter of Oddi though to a lesser degree and of shorter duration then opiates Nevertheless Utendorfer and Bergh have observed typical attacks of biliary colic following Demerol administration in persons with disease of the biliary tract Dreiling and Richman as well as Utendorfer and Bergh have found the analgesia obtained with procaine hydrochloride highly variable and unpleasant or dangerous side effects are not infrequent

Paravertebral sympathetic and splanchnic nerve block have also been recommended to relieve the pain in pancreatitis (Gage and Gillespie Paxton and Payne Pearson and Lungven Tejerina Fotheringham Cattell and Warren) Paravertebral nerve block is accomplished by the injection of a one per cent solution of procaine hydrochloride bilaterally into the paravertebral area in the interspaces from T_5 to T_{12} Unilateral and bilateral splanchnic nerve block is accomplished by the injection of 10 20 ml of one per cent procaine hydrochloride solution into the loose areolar tissue anterior to the body of the first lumbar vertebra

Epidural anaesthesia also has been advocated and seems to be a most effective method for controlling pain (Cattell and Warren Orr and Warren Berk and Kruperman) A 3 5 gauge ureteral catheter is introduced into the epidural space between L_1 and L and the tip of the catheter is maneuvered upward until it lies in the neighborhood of the interspace between T_3 and T Anaesthetic solutions can then be injected through the catheter as required It has the particular advantage that in recurrent disease of the pancreas the addiction to opiates is obviated

With these mechanical techniques for combating pain relief is obtained presumably by the interruption of impulses in the visceral afferent nerves which transmit the pain stimuli It should be pointed out that although relief of pain is effective with these

techniques their use does not appear to influence the course of the disease since as Jones points out a fatal termination may occur even though pain has been satisfactorily abolished

b) ***Control of Spasm of the Sphincter of Oddi*** As previously discussed spasm of the sphincter of Oddi and the pancreatico biliary ductal apparatus is often considered as either a primary inciting or a contributing factor in the development of episodes of acute pancreatitis These events usually include also spasm of the smooth muscle of the duodenum and upper digestive tract Measures directed at the muscle itself include (1) Inhalation of amyl nitrate (Dreiling and Richman Berk Doubilet and Mulholland) (2) Sublingual administration of 0 4 0 6 mg of nitroglycerin (Elman Cunha Bockus *et al*) or (3) The intravenous administration of 250 500 mg of aminophyllin (de Alvare) Unfortunately the duration of effects produced by these agents is short furthermore the presence of hypotension may mitigate against their use Gage and Gillespie have reported that calcium gluconate which is used primarily to replace the loss of serum calcium may also have an antispasmodic effect Certain of the agents used to relieve pain since they may act through the effector cells of the autonomic nervous system may also have some effect in the relief of muscle spasm

Two groups of autonomic blocking agents have also proved useful The first group exerts its principal action at the site of the effector cells supplied by the parasympathetic system namely the smooth muscle and exocrine gland cells their action is therefore parasympatholytic Atropine sulfate 0 4 0 6 mg parenterally repeated at three to four intervals is the best known agent of this type (Dreiling and Richman Berk Bockus *et al* Paxton and Payne Lium) Banthine an effective postganglionic blocking agent exerts its most marked effect on the upper gastrointestinal tract It is administered in dosage of 100 mg intravenously or intramuscularly It has a depressant effect on intestinal motility as well as on pancreatic secretion Probanthine has a similar effect when given parenterally in 15 0 30 0 mg doses These drugs if given intravenously should be administered in the form of a slow ... repeated at six hour intervals

Autonomic blocking agents of the second group exert their principal action on the autonomic ganglia where they effectively interrupt transmission of both sympathetic and parasympathetic impulses Tetraethyl ammonium chloride given slowly intravenously in dosage of 2-5 ml of a 10 *per cent* solution has been useful in the treatment of acute pancreatitis (Dreiling and Richman Berk Bockus *et al* Pearson and Lungren) Unfortunately its effects rarely last longer than one hour Jones states that in general methonium compounds are more effective blocking agents Hexamethonium bromide 250 mg every 12 hours administered by gavage has proved useful (Davies *et al*) However irregular responses to this agent occur due to erratic absorption in severely ill patients Therefore parenteral administration has a more predictable response A maximum of 25-50 mg may be given in fractional amounts slowly intravenously with frequent checks of blood pressure This dosage may be repeated after four to six hours The presence of hypotension does not render this form of therapy useless since measures for the control of shock remain effective even after their use

c) *Treatment of Shock* As pointed out in Part IV hypotension, decreased blood volume and hemoconcentration are common accompaniments of acute pancreatitis For the treatment of overt shock, Elliott *et al* recommend transfusions of whole blood and the administration of 100-200 ml of 25 *per* cent normal human serum albumin solution To these may be added dextran solution as well as other fluids as may be required The administration of normal serum albumin has much to recommend it not only is it effective in restoring blood volume but Kenwell and Wels believe it to have an antitryptic activity a view not accepted by Elliott *et al* The vascular collapse apparently due to trypsinemia justifies the cautious use of levophed as a slowly administered dilute solution (Jones) and cortisone acetate intramuscularly has been useful in certain instances (Stephenson *et al* Eskwith *et al*) When the need is urgent hydrocortisone 100 mg diluted in isotonic saline may be given intravenously and Jones believes that this may be a lifesaving procedure in some cases Adequacy of treatment of shock may be determined by

periodic measurement of blood volume blood pressure and hematocrit as well as by the establishment of a normal urinary output

Rush and Clifton have used SBI (soybean trypsin inhibitor) in dogs with experimentally induced pancreatitis in the belief that it specifically counteracts proteolytic activity and shock but this has not had sufficient clinical trial to establish it as a useful therapeutic agent According to Popper and Necheles the intravenous administration of dextran may reduce the morbidity of pancreatic fat necrosis They believe this effect of dextran is due mainly to an inhibition of pancreatic secretion Although their observations are experimental in dogs, they point out that this substance may be valuable in the treatment of acute pancreatitis pancreatic fistulas and traumatic and surgical injuries of the pancreas

d) ***Replacement of Fluid and Electrolytes*** In part this has been covered in the treatment of shock With the modern use of the flame spectrophotometer repletion of electrolytes can be accomplished under close laboratory control Nevertheless Edmondson *et al* point out that reduced sodium potassium calcium and chloride concentrations occur with such regularity that their replacement may be undertaken empirically Jones recommends the use of lactated Ringer s solution and Darrow s solution both of which are available commercially As previously noted not only must there be replacement of the initial losses of fluid directly related to the disease process but also that resulting from continuous nasogastric suction However when oliguria occurs caution must be exercised in the amount of fluid given Potassium loss may be gauged by the electrocardiographic changes and replacement instituted Losses of calcium are often so great that additional supplies of this ion must also be furnished in the form of 10 20 ml of a 10 per cent solution of calcium gluconate once or twice daily in order to avoid tetany Comfort has set up certain criteria for determining the necessity of administering potassium and calcium For serum potassium a level of less than 3 mEq per liter is considered an indication for repletion particularly if hypochloremic alkalosis is refractory He recommends one ampule of potassium chloride solution containing 1 49 gm (20 mEq) introduced into a liter of fluid and given intravenously

total amounts per day depend upon the degree of depletion and upon the behavior of values for serum potassium Again such therapy is given with great caution when urinary output is subnormal He recommends calcium repletion in the dose stated above when values for serum calcium fall below 8 mg per cent

e) *Temporary Suppression of Pancreatic Secretion* Since food intake is the most common stimulator of pancreatic secretion the patient with acute pancreatitis at bed rest should receive nothing by mouth In order to prevent gastric secretion from affecting pancreatic secretion continuous naso-gastric suction should be instituted early and maintained as long as indicated with periodic changing of the tube To accomplish this a soft Levin tube is passed into the stomach and the tip accurately located near the pylorus Continuous gentle suction is applied except in such brief instances as may be required to administer drugs by gavage

Various pharmacologic devices are also available for the elimination of neural and hormonal stimulation of pancreatic secretion Certain of the parasympatholytic and ganglionic blocking agents recommended for control of pain also depress acid secretion in the stomach and thus further aid in the elimination of the acid chyme from the duodenum These agents also suppress directly the neural stimuli to pancreatic secretion

The beneficial results from x ray therapy reported by Heacock and Cara and supported by the experimental observations of Rauch and Stenstrom have also been attributed to suppression of pancreatic secretion However as Jones points out the awkwardness of administration of such therapy in severely ill patients and the availability of other equally effective methods of control leave little to recommend this form of therapy

Siler and Wulsin point out that fluctuations in blood sugar between hyperglycemic and hypoglycemic levels also affect the exocrine secretory function of the pancreas and control of blood sugar levels may also be important in this regard

f) *Control of Distention* Abdominal distention in acute pancreatitis is most often due to ileus which may present a serious problem warranting prompt therapeutic attention The naso-

gastric suction used primarily to remove gastric secretion may be effective also in relieving such ileus and distention However, it may be necessary to intubate the small intestine to obtain adequate relief from this symptom

g) ***Prevention of Suppuration*** As has been pointed out in several chapters acute pancreatitis may develop initially on a suppurative basis or there may be a later development of suppuration within the pancreas and other sites in the peritoneal cavity from secondary infection of devitalized tissue Such considerations prompt the early and vigorous use of antibiotic therapy in every instance of acute pancreatitis particularly since in the great majority of cases it is not possible to obtain cultures of the diseased tissues Jones recommends the administration of 600 000 units of penicillin procain intramuscularly every twelve hours along with oxytetracycline hydrochloride or chlortetracycline intravenously in a dosage of 50 gm repeated at six hour intervals While in general oral administration might be more effective this route is not feasible because of vomiting ileus or the use of constant suction From the observations of Howard *et al* it may be deduced that antimicrobial agents not only reach the pancreas via the circulating blood but also readily enter the acinar cells and appear in the pancreatic secretion The effectiveness of antibiotics has been demonstrated by Donhauser who reported the following data

		Died	*Per Cent*
Pancreatitis treated medically	35		
No antibiotic	15	6	40 0
Antibiotic	20	3	15 0
Pancreatitis treated surgically	51		15 0
No antibiotic	31	17	54 8
Antibiotic	20	8	40 0

Such supportive therapy will result in the uninterrupted recovery of many patients with pancreatitis according to Jones However should peritonitis marked edema and bulging in the flanks evidence of acute pseudocyst formation or other events develop they may indicate the need for appropriate surgical intervention Furthermore Kirby *et al* have observed that late hemorrhage is a frequent cause of death in acute pancreatitis apparently as a result of enzymatic digestion of vascular walls

Such late hemorrhage may also require prompt adequate surgical drainage of tender abdominal masses However when possible definitive surgical procedures are best delayed until the acute attack subsides Specific procedures for such complications are discussed in the following section

h) *Management of Disturbances of Carbohydrate Metabolism* The effect of fluctuations in blood sugar levels on pancreatic secretion has already been mentioned Particularly important in this regard is the wellknown parasympathomimetic effect of hypoglycemia leading to increased secretory activity of the exocrine portion of the pancreas While glycosuria is common during an attack of acute pancreatitis the need for insulin therapy should be gauged by the blood glucose level Nevertheless insulin should be used with great caution since it may lead to hypoglycemic periods and may also aggravate an existing hypokalemia Furthermore special caution to avoid an insulin reaction is indicated when ganglionic blocking agents are employed since the sympathetic blood glucose mobilizing mechanism may be inoperative On the other hand the amounts of glucose solution administered in acute pancreatitis should also be carefully controlled since they may eventuate in hyperglycemic levels and the overstimulation of insulin secretion

The cessation of medical therapy following an attack of acute pancreatitis should be gradual and based on clinical signs of improvement When pain has subsided analgesic drugs are no longer required when the pulse rate and temperature have returned to normal limits and electrolyte balance established for a suitable period antibiotics and intravenous therapy may be discontinued when distention has disappeared and bowel sounds have returned suction may be discontinued and oral feedings begun With the naso gastric tube in place suction is discontinued and small feedings of broth and unsweetened fruit juices are started followed later by cream soups and skim milk Antiacids should be administered between feedings If pain does not recur with the first few feedings the nasal tube may then be removed Mild sedation in the form of oral phenobarbital 30 mg three times daily is advisable and banthine or probanthine should be

gastric suction used primarily to remove gastric secretion may be effective also in relieving such ileus and distention However it may be necessary to intubate the small intestine to obtain adequate relief from this symptom

g) ***Prevention of Suppuration*** As has been pointed out in several chapters acute pancreatitis may develop initially on a suppurative basis or there may be a later development of suppuration within the pancreas and other sites in the peritoneal cavity from secondary infection of devitalized tissue Such considerations prompt the early and vigorous use of antibiotic therapy in every instance of acute pancreatitis particularly since in the great majority of cases it is not possible to obtain cultures of the diseased tissues Jones recommends the administration of 600 000 units of penicillin procain intramuscularly every twelve hours along with oxytetracycline hydrochloride or chlortetracycline intravenously in a dosage of 50 gm repeated at six hour intervals While in general oral administration might be more effective this route is not feasible because of vomiting ileus or the use of constant suction From the observations of Howard *et al* it may be deduced that antimicrobial agents not only reach the pancreas via the circulating blood but also readily enter the acinar cells and appear in the pancreatic secretion The effectiveness of antibiotics has been demonstrated by Donhauser who reported the following data

Pancreatitis treated medically	35	*Died*	*Per Cent*
No antibiotic	15	6	40 0
Antibiotic	20	3	15 0
Pancreatitis treated surgically	51		15 0
No antibiotic	31	17	54 8
Antibiotic	20	8	40 0

Such supportive therapy will result in the uninterrupted recovery of many patients with pancreatitis according to Jones However should peritonitis marked edema and bulging in the flanks evidence of acute pseudocyst formation or other events develop they may indicate the need for appropriate surgical intervention Furthermore Kirby *et al* have observed that late hemorrhage is a frequent cause of death in acute pancreatitis apparently as a result of enzymatic digestion of vascular walls

Chapter 19

THE THERAPY OF COMPLICATIONS AND SEQUELAE OF ACUTE PANCREATITIS

While the treatment of an attack of acute pancreatitis is largely medical as discussed in the previous section the treatment of the complications and sequelae are largely surgical The latter are properly divided into two groups (1) Immediate or early complications which develop during the acute attack and (2) Late sequelae In the first group are such events as the localized collection of fluid intra abdominal abscess and acute pseudocyst or abscess formation in the lesser peritoneal cavity Siler and Wulsin point out that for these operation should be sufficient to assure adequate drainage but extensive exploration should be avoided Nevertheless they point out that there is divided opinion concerning patients admitted in circulatory collapse These cases almost always suggest the likelihood of extensive pancreatic necrosis One group believes there is a great tendency for the necrotic pancreas to perforate into the lesser peritoneal cavity and that drainage of this area through the foramen of Winslow or by a retroperitoneal approach is imperative A second group argues that operative interference cannot be tolerated by patients who are acutely ill and that surgical intervention only increases the mortality rate Some surgeons have even advocated cholecystectomy to reduce biliary pressure along with choledochostomy to drain the common bile duct (Mayo Archibald Judd)

Such operative intervention appears to be in disregard of the observations detailed in Part I that surgical procedures on the gastrointestinal or biliary tracts may actually precipitate an attack of acute pancreatitis in individuals exhibiting no evidence of pancreatic disease prior to surgery Thompson *et al* have recently reported that of 64 patients with acute pancreatitis following biliary surgery 62 had had choledochotomy and have concluded that this event is probably related to manipulation of the common duct They have therefore advised that the common bile duct be

continued by mouth three times daily As rapidly as can be tolerated the diet is increased to a bland one given in six small feedings per day Jones advises that the bland six meal diet the sedative three times daily and the administration of antispasmodic drugs should be continued indefinitely

Attention should also be directed during and following convalescence toward the prevention of recurrences At an appropriate time a careful investigation of the entire biliary apparatus should be instituted to determine the possibility of a Common Channel etiology The upper gastrointestinal tract should also be investigated for lesions such as diverticula which might occlude the pancreatic ductal apparatus or posterior duodenal ulcer penetrating into the pancreas Alcohol and other gastrointestinal irritants should be avoided Dietary measures should be instituted to prevent the ingestion of large quantities of food or drink and reasonable sized meals instituted as a prophylactic measure A program of mild sedation combined with antispasmodic and alkali therapy may prove helpful in some instances Arterial antispasmodics have been recommended (Paxton and Payne) and with patients in appropriate age groups serious consideration might also be given to instituting anticoagulant therapy in view of the frequency of vascular occlusion as demonstrated in this study and the importance of an adequate vascular supply However such therapeutic measures have not as yet been attempted by students of this disease

region and Hardy and Bowlin believe that a retroperitoneal abscess can be most often readily evacuated through a left flank incision They further point out that drainage of isolated scattered abscesses is rather unsatisfactory While surgical intervention is called for when a large abscess develops such procedures carry a high initial mortality Others have recommended that drainage be instituted for large intra abdominal accumulations of clotted blood which are particularly prone to form in the acute hemorrhagic disease but this too is accompanied by a similar high mortality

Fistulae often remain through such drainage sites if the patient is fortunate to survive According to Child and Donovan frequently patience over a period of months is required to observe spontaneous closure but operations performed early are neither wise nor necessary The skin about the fistula should be protected from excoriation by pancreatic juice by applying aluminum powder or paste

Pseudocysts of the pancreas may develop rapidly particularly in acute hemorrhagic disease of the pancreas or when the initiating cause is trauma Occasionally patients present with pseudocysts who give neither a history of antecedent acute hemorrhagic pancreatitis or traumatic incident These are probably instances of unrecognized pancreatitis In any event unless the clinical manifestations are such as to require immediate surgical intervention to halt blood loss they are best treated after the acute *symptoms have subsided And it is now generally accepted* that pseudocyst of the pancreas is best treated by surgical intervention Conservative therapy over a prolonged period may result in rupture into the peritoneal cavity with hemorrhage shock or in the case of superimposed infection – generalized peritonitis According to Koucky *et al* such rupture carries a mortality of about 60 per cent

Four forms of surgical intervention have been employed in the therapy of pseudocyst (1) Excision (2) Partial pancreatectomy (3) Marsupialization (external drainage) and (4) Internal drainage into the stomach jejunum or gallbladder depending upon the location of the lesion

explored only when necessary and with great care especially when bougies dilators or the scalpel is used in the sphincteric region They further point out that insertion of any mechanical device such as a long armed T tube across the sphincter is particularly dangerous Furthermore one may logically deduce that in a patient already suffering from acute pancreatitis such operative intervention might serve to intensify the disease process Thompson *et al* also emphasize that when such biliary tract surgery is followed by pancreatitis severe enough to be recognized the complication is usually fatal

1) ***The treatment of Immediate Complications of Acute Pancreatitis*** While the treatment of acute pancreatitis as detailed in the previous section is medical certain complications may arise in the course of an acute attack which require surgical intervention The development of pancreatic abscess single or multiple may require drainage pancreatic cysts may also have to be drained Gastric hemorrhage may require subtotal gastrectomy When a pancreatic abscess arises from a penetrating peptic ulcer subtotal gastric resection combined with partial pancreatectomy may be considered When possible operative intervention should be delayed until after the acute attack has subsided but situations may arise when such a delay might prove fatal One type of pancreatitis which may call for immediate surgical intervention is that due to trauma Child and Donovan have pointed out that abdominal paracentesis may help in deciding upon exploratory celiotomy in closed injuries to the pancreas A high amylase content of the withdrawn fluid or blood is diagnostic of injury to the pancreas They consider two general rules of operative management of importance (1) Badly damaged or ischemic pancreatic tissue should be removed and free drainage to the site of injury established and (2) Persistent bleeding and massive retroperitoneal hematomas commonly associated with pancreatic trauma must be dealt with effectively by ligature with nonabsorbable suture material such as cotton or silk

As pointed out in the previous section abscess formation may be discovered by the development of a palpable mass associated with fever Most commonly such masses occur in the left flank

high owing to leakage of the anastomosis and resulting peritonitis or to secondary infection of the cyst

Probstein has detailed the operative technique employed in transgastric cystogastrostomy One prerequisite for carrying out this procedure is that the cyst must be at least partially retrogastric and adherent to the posterior wall of the stomach most pseudocysts will meet this requirement The abdomen is explored through a midline vertical incision and the liver gallbladder and head of the pancreas examined An incision is made through the

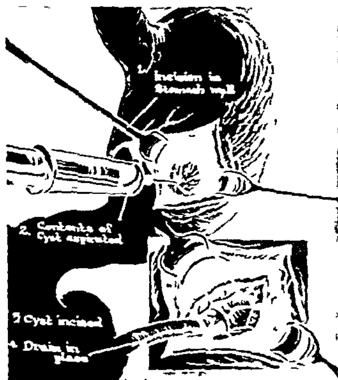


FIGURE 57 Figure shows various phases of the operative procedure in cystogastrostomy including the use of a catheter as employed only in the early cases. (From Probstein J C Pseudocyst of the pancreas Diagnosis and therapy A M A *Arch Surg* 69 425 1954)

anterior wall of the stomach and the cyst identified and aspirated as shown in Figure 57 A longitudinal incision about 2.5-3 cm in length is then made through the posterior wall of the stomach

In considering excision of a pseudocyst it is well to recall that according to Kune there is a 10 7 mortality with excision of all cysts of the pancreas which rises to 55 5 per cent if the intended extirpation proves impractical at operation This is particularly important in the case of pseudocysts because these lack a plane necessary for the removal of a cyst without injuring adjacent pancreatic tissue and removal therefore is difficult

Partial pancreatectomy is necessary only in the event there are multiple small cysts

Marsupialization entails the formation of an artificial sinus by which the pseudocyst communicates with the exterior (Johnson and Lee) It has the disadvantages of complications such as persistent fistula premature closure of the sinus tract with reformation of the cyst which may now become an abscess because of superimposed infection from the exterior a long period of illness and excoriation of the skin by pancreatic enzymes

In our opinion internal drainage appears to be the most desirable method for the treatment of pseudocysts since it offers adequate drainage without the disadvantages of marsupialization The objection has been raised in the case of transgastric cystogastrostomy that the reflux of gastric juice into the cyst may cause digestion of the wall but this has not materialized in the experience of one of us (Probstein) However Kafka has observed a single case of hemorrhage following transgastric cystogastrostomy and Maxeiner and Maxeiner have reported the development of a bleeding peptic ulcer at the anastomotic site A Roux Y jejunal limb anastomosis with a pseudocyst has also been utilized (Shumacker) but cystogastrostomy when it can be utilized has the advantage of simplicity

Transgastric anastomosis of such a cyst was first reported by Jedlicka (1923) and subsequently by Jurasz (1929) The literature contains reports of over fifty cases utilizing this procedure (Brandenburg *et al* Kune Scovel and Hollinger Zaoussis and others) Isolated reports of successful internal drainage by primary anastomosis of the cyst to other portions of the gastrointestinal tract and the gallbladder have also appeared in the literature (Hahn Walzel Kirschner) but the mortality has usually been

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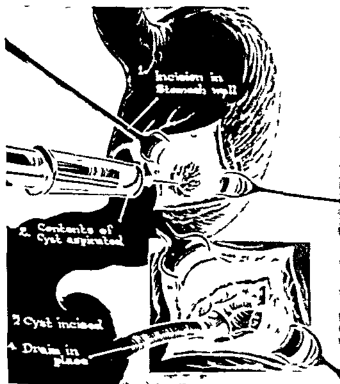


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years without recurrence The thirteenth case died suddenly of pulmonary embolism about six months after operation the specimen containing the obliterated cyst is shown in Figure 58

b) *Medical Management of Chronic Relapsing (Recurrent) Pancreatitis* Medical therapy in this complication has the following three primary objectives

1 Palliation and termination of the acute exacerbation
2 Prevention of further seizures and further pancreatic destruction
3 Control of external and internal pancreatic insufficiency as well as the more general nutritional disturbances

In general the approach to the first of these does not differ significantly from that of an initial attack of acute pancreatitis Usually such exacerbations are self limited subsiding after one or several days and there is presumably only edema and small areas of necrosis Management as a rule consists of providing rest in bed limiting the oral intake of fluids and the administration of adequate sedation and appropriate fluids and electrolytes parenterally With more severe prolonged recurrences greater attention must be given to fluid and electrolyte imbalances ileus with nausea vomiting and abdominal distention shock and secondary infection as previously detailed for an acute attack

Following the cessation of a seizure medical means for preventing recurring painful attacks and progression of the disease are few and of limited value They consist of adherence to a bland diet avoidance of over eating and complete abstinence from alcohol or other irritating beverages

The control of pancreatic insufficiency which develops as destruction of the pancreas progresses requires control of the diabetes and the excessive losses of fat and nitrogen with their associated abdominal discomfort and loss of weight Steatorrhea and azotorrhea may be controlled by a dietary program and by the use of pancreatin Caloric losses may require a greater caloric intake at times as much as 70 80 per cent in excess of the basal requirement The intake of large amounts of protein is particularly desirable and is well tolerated but the intake of large amounts

into the cyst The latter is explored with a finger and a biopsy specimen obtained to rule out a neoplastic cyst Multiple interrupted absorbable sutures are then placed circumferentially for hemostasis and to evert the gastric mucosa Early in the use of this procedure a large Pessar catheter was placed in the cyst cavity and brought out through the stomach and the anterior abdominal wall but this procedure has been found unnecessary The anterior wall of the stomach and the abdominal wound are then closed without drainage

Of the group of 13 cases which have been so treated by Probstein four have now gone five years one seven years one eight years three for three years and three between one and three



FIGURE 58 Gross specimen of stomach and pancreas removed at post mortem examination from patient who died six months after cystogastrostomy of pulmonary embolism The cyst area has been replaced by dense gray fibrous tissue and all that remains of the cyst cavity is a narrow tract containing a probe (arrow at *P C*) A tiny opening in the gastric mucosa which communicated with this tract is shown at point of arrow adjacent to S (From Probstein J G Pseudocyst of the pancreas Diagnosis and therapy *A M A Arch Surg* 69 425 1954)

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There are two purposes for removing disease of the biliary tract (1) to relieve symptoms due to disease of this tract and (2) to prevent the potentially hazardous complications to the pancreas The removal of the normal appearing gallbladder has not been helpful in preventing recurring attacks according to Gross and Comfort but Zollinger in discussing a report by Elliott *et al* has recently recommended such a procedure in order to obliterate a reservoir for the possible future incubation of a lethal mixture of bile and pancreatic juice Particularly important is the removal of stones in the common duct and the removal of a gallbladder containing calculi cases with a stone in the common duct with jaundice neglected over a period of years are particularly benefited Gross and Comfort state that while removal of disease of the biliary tract in the well established case of recurrent disease may sometimes be followed by relief this procedure fails too often to affect the frequency and severity of the recurrent attacks

External and internal drainage of the common bile duct are commonly employed to reduce pressures in the common bile and pancreatic ducts in the presence of a common channel Cholecystostomy one of the earliest procedures of this type has been largely abandoned although occasional relief from painful seizures has followed Prolonged external drainage of the common bile duct by use of a T tube has the disadvantage of not providing permanent drainage (Maimon *et al* Coffey and Blumberg Cogswell Partington Priestley Warren Waugh) Internal drainage if permanent, is theoretically superior (Mallet Guy Horton) Various types of internal drainage have been employed including side to-side anastomosis between the gallbladder and the stomach or jejunum side to-side anastomosis between the common bile duct and duodenum or Roux Y type of anastomosis between the gallbladder and jejunum

Sphincterotomy first advocated by Archibald and currently in wide use due to the impetus given by the investigations of Colp *et al* and Doubilet and Mulholland has been employed primarily to relieve spasm of the sphincter or inflammatory obstruction in the ampullary region and thus to correct the normal channel

of fat may well increase the diarrhea and abdominal discomfort Gross and Comfort recommend a dietary intake of fat restricted to 50-70 gm per day with ingestion of 120 gm of protein and up to 450 gm of carbohydrate to compensate for the calories lost by restriction of fat Concentrated triple strength pancreatin as enteric coated tablets (0 3 gm or 5 grains each) is given in effective doses As much as 5 gm of pancreatin with each meal is sometimes necessary to reduce significantly the losses of fecal fat and nitrogen and to permit the ingestion of sufficient quantities of fat to make the diet palatable and to reduce abdominal discomfort Often the patient can best determine his own effective dose Sorethytan monooleate (Tween 80) has also been tried in this regard and has not proved of value (Comfort) Multivitamin capsules should be prescribed particularly when the patient is malnourished and the intake of food is restricted Anemia may require iron supplementation and occasionally whole blood transfusion Insulin therapy may be required for control of the diabetes but the latter may constitute only a temporary complication and periodic re evaluation of the diabetic state should be carried out

c) *Surgical Therapy of Chronic Relapsing (Recurrent) Pancreatitis* A large number of surgical procedures have been employed in the treatment of recurrent disease and these reflect the continued efforts to prevent progression of the disease and to prevent and relieve pain In many cases the physician and surgeon must be willing to settle for temporary relief even partial palliation always with the hope that the disease eventually will become quiescent as it sometimes does The surgical procedures employed may be divided into the following groups according to the ends which they are designed to attain

1 Procedures for removing disease of the biliary tract
2 Procedures for external and internal drainage of the common bile duct
3 Operations on the pancreas itself for removal of disease
4 Procedures designed to decrease pancreatic secretion
5 Procedures for the relief of pain

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of internal drainage Gross and Comfort point out that the results of sphincterotomy have been somewhat encouraging but follow up studies covering periods of over five years are not yet available The results appear to be similar to those obtained with external and internal drainage

Doubilet and Mulholland recommend that sphincterotomy be performed after the acute phase has subsided The cystic duct is isolated and cholangiographic studies are carried out through a needle inserted into it In the absence of a gallbladder the needle is inserted into the common duct Ten ml of 0 1 N HCl is injected through a previously passed Rehfus tube to produce spasm of the sphincter of Oddi and cause diodrast to enter the pancreatic ductal system The gallbladder is then removed the common duct opened supraduodenally and the sphincter of Oddi cut endocholedochally if the sphincterotome enters the duodenum readily The common duct is then closed and a small rubber tube placed down in it If the sphincterotome is arrested at the papilla a 3 mm incision is made in the anterior duodenal wall over the tip of the instrument and the papilla riding on the end of the instrument is made to protrude through this small incision The sphincter is then sectioned under vision the instrument withdrawn and the opening in the duodenal wall closed A T tube is placed in the common duct if the patient is to be studied for proof that function of the sphincter has been destroyed pancreatic reflux prevented and duodenal reflux not permitted On the tenth day cholangiographic studies are performed to confirm the absence of residual stones to show that the sphincter does not react to acid and to prove that the duodenal wall is intact Kymographic tracings may be done the following day to confirm these observations

Jones *et al* have recommended the resection of a wedge of the lower end of the common duct and duodenal wall as a means of diminishing the resistance to the outflow of bile and pancreatic juice The rationale for this procedure is based on the idea that contraction of duodenal musculature may constrict the intramural portion of the common and pancreatic ducts and that such an obstruction could be responsible for pancreatitis in a patient without a common channel

Priestley has reviewed the results of external and internal biliary drainage in 100 cases of recurrent disease External drainage in 72 cases gave complete relief in 52 per cent partial relief in 22 per cent and no relief in 26 per cent Internal drainage afforded complete relief in 39 per cent partial relief in 39 per cent and no relief in 22 per cent The follow up period in this series was 5 to 19 years in two-thirds of the cases and 3 to 5 years in the remainder Better results were obtained when disease of the biliary tract was present and before the sequelae of pancreatitis had appeared

Operations on the pancreas itself include removal of pancreatic calculi followed by T tube drainage marsupialization as well as other procedures for the external and internal drainage of pseudocysts presented previously partial or complete pancreatic resection and pancreatico jejunostomy Removal of large stones from the main pancreatic duct has been followed by good results in a limited number of patients especially when the stones were intraductal for the most part (Elason and Welty Rhoades *et al*) Partial or complete resection of the pancreas is usually performed only after more conservative measures have failed and when disability is marked There is a higher mortality rate with these procedures and a greater morbidity Partial pancreatectomy is so performed that the external pancreatic secretion from the remainder of the gland drains into the gastrointestinal tract thus preventing as far as possible maldigestion and malabsorption (Warren Rhoades *et al* Whipple Cattell and Warren) Gross and Comfort believe the results have been gratifying particularly in those cases in which partial resection was limited either to the head or to the tail Total pancreatectomy has been employed only in the exceptional case in which all other measures have failed (Rhoades *et al* Whipple Waugh Waugh *et al*) Du Val has utilized decompression of the obstructed pancreatic ducts by pancreatico jejunostomy with good results in 20 per cent of 25 patients followed for a period of up to three years

Procedures utilized to decrease pancreatic secretion are partial gastrectomy vagotomy sympathectomy and ligation of the duct of Wirsung They have been employed in the belief that

pancreatic secretion aggravates pancreatitis by increasing the intraductal pressures Failures have been reported with partial gastrectomies (Cattell and Warren Johnson), as well as suc cesses (Richman and Colp) Gross and Comfort state that they have not seen the course of the disease halted when partial gas trectomy has been carried out for a concomitant duodenal ulcer Vagotomy alone has been followed by improvement in a few cases (Johnson) and relief has been obtained by transthoracic vagectomy and sympathectomy (Reinhoff and Baker) On the other hand failures have also been reported (Rack and Elkins) The possibility of the addition of untoward post vagotomy symp toms superimposed on those of chronic pancreatitis have prob ably acted as a deterrent in the use of these procedures

Sympathectomy has been the chief operative procedure for the relief of pain (Rhoades *et al* Reinhoff and Baker Rack and Elkins de Takats *et al* Hyman and Burton Hurwitz and Gur witz Connolly and Richards Smithwick Mallet Gug and de Beau jeu Martin and Canseco) It is generally employed when other measures have failed and when pain is frequent and disabling Such relief ordinarily lasts only for a few years and to date appar ently no patients have experienced relief lasting more than five years

Cannon has advocated transduodenal or extraduodenal liga tion of the duct of Wirsung for the relief of pain on the premise that pancreatic duct ligation will result in destruction of pan creatic exocrine activity and that the latter is responsible for the pain in chronic relapsing pancreatitis He has reported the results of these procedures in six cases one of which showed some relief in one the results were equivocal and in one no benefit was de rived A fifth case was too recent at the time of the report to be properly evaluated and a sixth died of pulmonary embolism It is doubtful that exocrine function can be destroyed by this pro cedure since secretion may continue through the duct of San torini if it is present and patent as well as through accessory ducts In any event this procedure has received insufficient usage to be properly evaluated

While many of these procedures appear to be justified even when they afford only temporary or incomplete relief their true

evaluation is complicated by a number of considerations Not uncommonly the occurrence of exacerbations seem to disappear spontaneously, and in some cases remissions may last for long periods The number and the severity of the attacks vary greatly in any particular case as well as from patient to patient Since the natural history of the disease has not been adequately studied valid statistics as to the frequency of spontaneous remissions are not available The results with operative procedures on the biliary tract for chronic relapsing pancreatitis compare poorly with the results obtained when surgery is performed on the biliary system for its own symptoms The same is true with regard to the results with partial gastrectomy for pancreatic disease as compared with the same procedure for duodenal or gastric ulcers Nevertheless until better therapeutic measures are available with which to combat the symptoms for which these surgical procedures are designed they appear to offer the best measures for palliation and to prevent further pancreatic destruction

SUMMARY

In order to properly evaluate the effectiveness of therapeutic measures it is necessary to recall the evolution of current methods and the changing mortality rates which have evolved with them Prior to the widespread use of the serum amylase test as a diagnostic tool pancreatitis was diagnosed with a significant degree of certainty only at surgery or at autopsy Siler and Wulsin have given mortality figures representative of that period as follows

Edematous pancreatitis	30 per cent
Hemorrhagic and necrotizing pancreatitis	60-70 per cent
Suppurative pancreatitis	50 per cent
All types combined	50 per cent

Improvement in diagnostic procedures is responsible for some of the improvement in mortality statistics for mild acute pancreatitis with a low mortality rate is now commonly recognized and would dilute the mortality figures Nevertheless mortality data in which there is separation of inflammatory pancreatic disease into its various types show a greater percentage of recovery of severe cases than formerly (Kirby *et al* Siler *et al*) Furthermore Kirby *et al* have directed attention to a changing

cause of death in acute pancreatitis as a consequence of improved therapy and longer survival. In patients treated before 1946 death resulted early from circulatory collapse while in those treated after 1946 survival was longer and death occurred more frequently from secondary hemorrhage or sepsis. Despite the effectiveness of modern therapy, Machella and also Fallis have concluded that there appears to be an irreducible mortality, the magnitude of which is in the neighborhood of 10 per cent.

The tabulation below from selected reports affords a comparison of early surgical as opposed to conservative therapy and indicates that mortality with medical therapy is about half that with early operative intervention. However, such data may not be entirely reliable since they are undoubtedly influenced by the proportion of severe cases in any particular study. Thus in reviewing reports containing mortality data Roberts *et al* state that the range for acute pancreatic necrosis is between 16 and 70 per cent with an average of 50 per cent, while with acute interstitial pancreatitis the range is between zero and 41 per cent with an average of 15 per cent. Moreover, Pfeiffer and Miller operated on 16 patients with early or edematous pancreatitis without fatality, whereas the mortality in eleven operated patients with severe pancreatitis was 46 per cent. Nevertheless, Pfeiffer and Miller admit that conservative therapy in the cases with early or edematous disease of the pancreas might also have resulted in no fatalities.

Author	*Mortality with Operative Therapy*	*Mortality with Conservative Therapy*
Finney (1933)	37.0	
Fallis (1939)	46.2	6.3
Pratt (1940)	54.0	25.0
Morton (1940)	49.03	
Lewison (1940)	50.0	
Lampson (1942)	33.0	5.0
Whipple (1948)	34.0	15.0
Paxton and Payne (1948)	44.7	5.0
Donhauser (1954)	49.0	25.8

Priestley *et al* have recommended that a more aggressive early surgical approach be re-evaluated since conclusions as to the ineffectiveness of surgical intervention are based on experi

ences before the advent of effective antimicrobial therapy Mitigating against a re evaluation of surgical measures are the many considerations discussed in Part I regarding pathogenesis Surgical measures may appear to have a degree of logic in those cases which develop on either an organic or functional obstructive basis for the treatment of which procedures are available However even if one takes the most optimistic view as regards the frequency of pancreatitis on such a pathogenic basis it probably cannot account for more than about one third of the cases It is difficult to visualize what surgical procedures might be instituted for a fulminating hemorrhagic pancreatitis in which there is no evidence of obstruction of the biliary or pancreatic ductal systems Furthermore as has been pointed out surgical procedures in the region of the biliary tract and pancreas may precipitate an attack of pancreatitis in patients with no antecedent disease of the pancreas and it seems only logical to assume that operative manipulation of this region in patients who already have acute pancreatitis might serve to intensify the disease process It is also difficult to appreciate how antibiotic therapy would improve the effectiveness of early surgical intervention since when operative procedures were carried out formerly death was most frequently due to circulatory collapse rather than complicating infections Nevertheless antibiotic therapy has proved effective in increasing survival rates in patients with acute pancreatitis who develop abscesses requiring surgical intervention for purposes of drainage

As has been pointed out the majority of students of this disease have concluded that medical therapy is the most effective approach in early acute pancreatitis On the other hand surgical intervention may be required for certain of the immediate complications as detailed herein and for certain specific purposes in the treatment of chronic relapsing (recurrent) pancreatitis

Part V

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CONCLUSION

As Bell has pointed out in a broad sense pancreatitis includes all inflammations of the pancreas without regard to etiology This is the sense in which this disease designation has been employed here Such a broad view appears justified since once the disease has been established the pathologic changes or the clinical manifestations often do not permit a differentiation as to the nature of the causation As with any disease which may be caused by a broad spectrum of etiologic factors the range of variation in intensity may be considerable and we have therefore divided the cases into three groups as follows (1) Those in which acute pancreatitis was considered the principal cause of death (2) Those in which the pancreatic disease was an important contributing cause of death and (3) Those cases in which acute pancreatitis was only an incidental finding at autopsy without any direct relation to the cause of death The incidence of acute pancreatitis without regard to intensity is about 44 per thousand cases but the frequency of pancreatitis of sufficient severity to cause death is only about 5 per thousand The corrected sex frequency in most studies shows a slight predominance of females but the difference is not striking While the disease may occur at any age including infancy most of the severe cases occur during the fifth decade of life

At various times in the evolution of an understanding of the multiplicity of factors which may precipitate inflammatory disease of the pancreas one or another factor has been stressed sometimes to the exclusion of others It has been our purpose here to discuss all of the etiologic factors considered in the literature whether *real or hypothetical* and to place *them in proper* perspective Part I has dealt largely with this aspect of the subject and thus serves to point up the complexity of precipitating causes which in any given case may often be multiple Despite such considerations the present series has lacked sufficient definitive information in about one third of the cases to permit a conclusion as to cause If suggestive evidence was included in

creatic ferments There may be only mild disease progression from mild to severe disease or the latter may obtain from the outset As to destructive processes while considerable emphasis has in the past been placed on the role of trypsin in the production of parenchymatous necrosis it appears more likely that all or almost all of the pancreatic proteolytic enzymes play a role Lipase is responsible for the fat necrosis and vascular necrosis for the hemorrhage Particularly important as regards vascular digestion are the enzymes collagenase and elastase present in the pancreas The former requires no activation and is probably dependent only upon removal of protective mechanisms or transport to sites where a susceptible substrate resides The importance of elastase rests on its ability to destroy the elastic membranes of vessels the structures which offer the most effective line of resistance to vascular rupture Thus while collagenase and trypsin may injure vessels in part it is the action of elastase which in the final analysis is responsible for the hemorrhagic component of the disease and which may convert a relatively mild case into a fulminating hemorrhagic form The biochemical reactions which are responsible for calcification of fat and parenchyma have been described and these as well as fibrosis represent processes of healing On the other hand the formation of calculi within ducts appears to be of an entirely different nature probably not related to antecedent inflammatory disease of the pancreas

These patho physiologic changes also exert systemic influences Alterations in leucocytes blood volume blood coagulability serum electrolyte levels carbohydrate metabolism serum lipids and serum enzymes have all been considered as have also effects on the function of the liver kidney heart respiratory apparatus gallbladder and gastrointestinal tract In some instances these effects are due to a diminished concentration of certain substances from the blood related to destructive processes in the pancreas or loss of pancreatic function in others as in the case of changes in serum enzyme levels substances are released from necrotic pancreatic tissue and are absorbed into the blood stream Still other effects may be produced by irritation of nerves or by the embolization of necrotic tissues through

addition there remained about 10 per cent of cases in which no clue as to etiology could be found

In Part I we have classified and discussed the nature of precipitating causes and have utilized our 163 autopsied cases to illustrate the characteristics and frequency of these etiologic agents The latter have been placed in seven basic categories i e Infectious Obstructive (biliary and/or pancreatic) Metabolic Toxic or Chemical Traumatic Vascular Allergic and Idiopathic The causes of complications have also been discussed and these are usually due either to a dissemination of products of the pancreatic disease or to sequelae resulting from healing processes within the pancreas

Once initiating causes become effective they set up a chain of events within the pancreas which progress more or less autonomously The nature of this autonomy relates to certain normal functional characteristics of the organ The normal function of the pancreas is a precarious one since it contains enzymes capable of accomplishing self digestion these are proteolytic lipolytic and amylolytic in nature However there are also mechanisms which exert a protective action In addition to protective mucin supplied by glands residing in the walls of ducts many of the potentially destructive ferments exist in the pancreas as inactive precursor forms and enzyme inhibitors are also present The idea has been presented that under normal conditions the destructive forces and protective mechanisms are in balance and that any condition which intensifies the former or diminishes the effectiveness of the latter can lead to inflammatory disease of the pancreas Thus the various etiologic categories presented in Part I act essentially to upset this balance and the activated enzymes may then proceed to produce the various destructive changes in the pancreas which are characteristic of pancreatitis Mechanisms which are capable of such enzyme activation have been discussed in Part II

✓ Injurious effects on the pancreas range from mild edema and inflammation to extensive necrosis and hemorrhage Minimum reaction may be produced by mild irritants while more extensive processes are the results of activities of the various pan

creatic ferments There may be only mild disease progression from mild to severe disease or the latter may obtain from the outset As to destructive processes while considerable emphasis has in the past been placed on the role of trypsin in the production of parenchymatous necrosis it appears more likely that all or almost all of the pancreatic proteolytic enzymes play a role Lipase is responsible for the fat necrosis and vascular necrosis for the hemorrhage Particularly important as regards vascular digestion are the enzymes collagenase and elastase present in the pancreas The former requires no activation and is probably dependent only upon removal of protective mechanisms or transport to sites where a susceptible substrate resides The importance of elastase rests on its ability to destroy the elastic membranes of vessels the structures which offer the most effective line of resistance to vascular rupture Thus while collagenase and trypsin may injure vessels in part it is the action of elastase which in the final anlysis is responsible for the hemorrhagic component of the disease and which may convert a relatively mild case into a fulminating hemorrhagic form The biochemical reactions which are responsible for calcification of fat and parenchyma have been described and these as well as fibrosis represent processes of healing On the other hand the formation of calculi within ducts appears to be of an entirely different nature probably not related to antecedent inflammatory disease of the pancreas

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Injurious effects on the pancreas range from mild edema and inflammation to extensive necrosis and hemorrhage Minimum reaction may be produced by mild irritants while more extensive processes are the results of activities of the various pan

elements in the pancreas with advancing age just as in most other organs and here too it probably reflects a response to progressive vascular impairment The extent to which such changes influence the susceptibility of this organ to inflammatory disease remains unsolved Thus certain changes in the pancreas with aging probably secondary to pancreatic arteriosclerosis may on the one hand serve to diminish the effectiveness of protective mechanisms and leave the pancreas in a susceptible state as regards destructive forces while on the other a loss of acinar tissue may diminish the output of potentially destructive enzymes

The pathology of death in pancreatitis also remains elusive Loss of blood volume *release of a toxin hypertrypsinemia and* tetany are among the chief phenomena which have received consideration but the case for any of these is far from convincing Instances of sudden death from pancreatitis without significant blood loss and without sufficient time for the development of a toxemia or tetany stand as evidence against these factors and thus *the problem remains unsolved*

The complications and sequelae of pancreatitis can be divided into those complications which are essentially part of the initial disease process such as local collections of blood or fluid abscess or pseudocyst and those which occur because the initial destruction and healing has conferred a state of susceptibility on the *pancreas* to recurrent episodes While abscess formation is more common in suppurative pancreatitis it may occur with other forms and its location is determined by its site within the pancreas and the relations of adjacent anatomic structures Thus perinephric abscess has been common in our experience with pancreatitis involving the tail and abscess formation in the lesser *omental* bursa may occur when the head is involved Pseudocyst is a term reserved for encapsulated collections of fluid or blood and again the anatomic site at which it develops is determined by its location in the pancreas and the relation of the latter to adjacent anatomic structures Calculus formation in pancreatic ducts apparently occurs in about one fourth of the cases of recurrent pancreatitis *although it occurs infrequently* in a general autopsy population It seems unlikely however that

the open ends of digested lymphatic and blood vessels With subsidence of the acute disease there may be no patho physiologic evidence of residua but if considerable pancreatic tissue has been destroyed as often occurs with repeated episodes there may be evidence of pancreatic insufficiency characterized by a loss of digestive activities dependent upon pancreatic enzymes

Part III has dealt largely with the anatomic counterparts of the physiologic processes discussed in Part II It has been pointed out that the basic changes in pancreatitis are those of edema suppuration and necrosis These may be complicated by vascular phenomena such as infarction and hemorrhage certain of the latter processes may in some instances initiate the pancreatitis by virtue of the associated necrosis which may lead to the activation of trypsin and other enzymes Changes in the specific tissue components of the pancreas such as fat acini ducts and vessels have also been described Particularly worthy of re emphasis are certain gaps in our knowledge of the pathology of pancreatitis The pattern and mode of dissemination of fat necrosis requires further study We have elucidated some evidence which appears to indicate that squamous and goblet cell metaplasia are alterations which probably are protective in nature rather than a cause of pancreatitis The phenomenon of squamous metaplasia in particular has heretofore been considered by almost all investigators as a cause of pancreatitis because in some instances it may progress to complete obliteration of some ducts Goblet cell metaplasia appears to have been described here for the first time and the evidence for a protective effect of its secreted mucin has been elucidated in Part II Both types of metaplasia show a similar age distribution curve Further study of the nature and significance of these changes also appear indicated The vascular alterations are of two kinds (1) those which occur independent of pancreatitis but which may exert an influence on the development of the disease particularly if they initiate hemorrhage or infarction and (2) those which are the result of the digestive effect of enzymes during an attack of acute pancreatitis The roles of each type in the initiation and progression of the disease require further study and amplification There appears to be a progressive increase in connective tissue

sion there are those which simulate gall bladder disease intestinal obstruction peptic ulcer or alcoholic gastritis and abdominal tumor In addition there are cases with complaints which lack sufficient definition to arouse suspicion of pancreatic disease as well as others which may be asymptomatic There is thus a great range in intensity from case to case at one extreme are those with essentially symptomless disease sometimes discovered incidentally at autopsy while at the other extreme are the instances of fulminating disease with sudden or rapid death

The clinical manifestations of complications and sequelae are also properly divided into the immediate complications and later sequelae The symptoms of the former in addition to those recited above for acute pancreatitis are attributable in large part to symptoms of pressure from a mass The latter is actually an abscess pseudocyst or localized fluid or hematoma which exert pressure on adjacent viscera and are manifested on x ray by organ displacement The later complications are due either to healing processes or to persistent biliary tract disease which may have caused the pancreatitis in the first instance Among the latter complications are intestinal obstruction due to adhesions fistula formation which may result from pointing and drainage of an abscess into an intestinal segment or from marsupialization of a pseudocyst biliary tract obstruction either as a result of compression of the common bile duct by a cirrhotic head of the pancreas or due to a common duct stone and pyelphlebitis with liver abscess formation By far the most frequent however is recurrent acute pancreatitis with eventual replacement of both exocrine and endocrine elements of the pancreas by inflammatory and scar tissue The latter results in persistent pain because of inflammation and compression of nerves by scar tissue insufficiency of pancreatic enzymes with symptoms of steatorrhea, azotorrhea and amylorrhea and insulin insufficiency as a result of destruction of islets of Langerhans Again x ray of the abdomen may be useful in detecting stones in pancreatic ducts and cholangiographic studies may be helpful in detecting biliary tract disease One of the most striking statistical features of recurrent pancreatitis is its 3 6 fold predominance in the male in contrast

it is a product of antecedent pancreatitis it more likely develops on the basis of an unrelated disease such as hyperparathyroidism but once established it may become an etiologic factor in recurrent attacks

The clinical manifestations of acute pancreatitis presented in Part IV are a more or less direct reflection of the physiologic and pathoanatomic phenomena elucidated in Parts II and III Thus the intensity and distribution of pain have been related to inflammatory involvement of nerve supply pancreatic capsule extension of inflammation to the peritoneum and involvement of the biliary tract Abdominal distention has been attributed to paralytic ileus the accumulation of fluid in the peritoneal cavity or to constipation related to a loss of intestinal motility Shock evidently occurs when there is a sufficient loss of blood volume either because of intensity of pain or formation of pancreatic exudate or hemorrhage Significant elevations in temperature may be due to septic processes or to absorption of split products of protein and icterus to compression of the common bile duct as it passes through the edematous head of the pancreas Tetany when it occurs is due to a lowering of blood calcium because of its mobilization in foci of fat necrosis The laboratory tests which are commonly used to establish a diagnosis of acute pancreatitis are based on certain of the alterations in the blood and effects on other organs documented in Part II The electrocardiographic findings are also probably related to alterations in serum potassium or epicardial fat necrosis Those physical findings in acute pancreatitis which do not have a common basis with certain of the symptoms listed above are attributable either to localized collections of fluid blood or abscess material or to certain skin alterations which result either from extension of hemorrhage from the region of the pancreas or to the alterations in blood coagulability

A number of other diseases may mimic acute pancreatitis and a detailed differential diagnosis has therefore been presented Perhaps the perplexity of this problem is best expressed in the clinical classification of acute pancreatitis into five types by Paxton and Payne who have shown that in addition to the typical text book type of case which may resemble coronary occlu

sion there are those which simulate gall bladder disease intestinal obstruction peptic ulcer or alcoholic gastritis and abdominal tumor In addition there are cases with complaints which lack sufficient definition to arouse suspicion of pancreatic disease as well as others which may be asymptomatic There is thus a great range in intensity from case to case at one extreme are those with essentially symptomless disease sometimes discovered incidentally at autopsy while at the other extreme are the instances of fulminating disease with sudden or rapid death

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to initial attacks of acute pancreatitis which show a slight pre dominance in females

Finally in Part V therapeutic measures have been considered It has been emphasized that the treatment of acute bouts of pancreatitis is primarily medical while the treatment of the com plications and sequelae are largely surgical Certain of the imme diate complications of acute attacks sometimes also require sur gical intervention Medical measures are specifically aimed at the relief of pain, control of spasm of the sphincter of Oddi the treatment of shock the replacement of fluid and electrolytes the temporary suppression of pancreatic secretion the prevention and control of distention the prevention of suppuration and the control of disturbances in carbohydrate metabolism Not only are the purposes of such therapeutic measures discussed but in most instances the mode of action of therapeutic agents are also pre sented

The treatment of the immediate complications of acute pan creatitis largely involve the drainage of local accumulations of fluid abscess material or blood On the other hand the surgical treatment of pseudocyst entails rather specialized procedures, the most effective of which in our experience is cystogas trostomy

There are both medical and surgical aspects to the treatment of chronic relapsing (recurrent) pancreatitis The medical man agement is aimed first at the palliation and termination of acute exacerbations as they arise and secondly at the prevention of further seizures and further pancreatic destruction Eventually exocrine and/or endocrine pancreatic insufficiency may develop and then the management entails largely replacement of pan creatic enzymes in the gastrointestinal tract and insulin in the cir culating blood The surgical management of recurrent pancreatic disease has as its aims the removal of disease of the biliary tract establishing adequate drainage of the common bile duct either by internal procedure or externally removal of disease of the pancreas or establishing adequate drainage through the pan creatic duct the diminution of pancreatic secretion and the re lief of pain persisting even between acute exacerbations

A presentation of this type serves several important purposes In the first place it focuses attention on a disease the importance and frequency of which may not be generally appreciated, although there seems to be an increasing awareness of it in recent years Secondly it permits the acquisition of perspective and the evaluation of the complexities of etiology pathogenesis diagnosis and therapy And finally, it serves as a means of focusing attention on problems for future study

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